Synthesis and Reactivity of Pyridine Substituted α-Diazocarbonyl Compounds and Exploration of Rhodium Carboxylates as Asymmetric Catalysts

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A thesis presented for the degree of

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To

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Brian Feerick

Abstract

The primary objective of this thesis was the preparation of a series of pyridine-containing α-diazocarbonyl compounds and subsequent investigation of the reactivity of these compounds on exposure to transition metal catalysts. In particular, the reactivity of the pyridyl α-diazocarbonyls was compared to that of the analogous phenyl α-diazocarbonyl compounds to ascertain the impact of replacement of the phenyl ring with pyridine.

The first chapter initially provides a brief introduction into α-diazocarbonyl chemistry, comprising a compendium of well-established and recently developed methods in the preparation of these compounds, as well as an outline of the reactivity of these versatile substrates. The substantive element of this introductory chapter comprises a detailed review focused on transition metal-catalysed transformations of heterocyclic α-diazocarbonyl compounds, highlighting the extraordinary diversity of reaction products which can be accessed. This review is undertaken to set the work of this thesis in context.

The results of this research are discussed in the second and third chapters together with the associated experimental details, including spectroscopic and analytical data obtained in the synthesis of all compounds during this research. The second chapter describes the preparation of a range of novel pyridine-containing α-diazocarbonyl compounds *via* a number of synthetic strategies including both acylation and diazo transfer methodologies. In contrast to the phenyl analogues, the generation of the pyridine α-diazocarbonyl substrates was complicated by a number of factors including the inherent basicity of the pyridine ring, tautomerism and existence of rotamers. Rhodium- and copper-mediated transformations of the pyridine-containing α-diazocarbonyl compounds is discussed in detail displaying very different reactivity patterns to those seen with the phenyl analogues; oxidation to 2,3-diketones, 1,2-hydride shift to form enones and oxonium and sulfonium ylide formation/rearrangement are prominent in the pyridyl series, with no evidence of aromatic addition to the pyridine ring.

The third chapter focuses on exploration of novel chiral rhodium(II) catalysts, developed in the Maguire team, in both intermolecular cyclopropanations and intramolecular C–H insertion reactions. In this chapter, the studies are focused on standard α-diazocarbonyl compounds without heteroaryl substituents. The most notable outcome was the achievement of high enantiopurities for intramolecular C–H insertions, which were competitive with, and even surpassed, established catalyst systems in some cases. This work has provided insight into solvent and temperature effects on yields as well as enantio- and diastereoselectivity, thereby providing guidance for future development and design of chiral rhodium carboxylate catalysts. While this is a preliminary study, the significance of the results lie in the fact that these are the first reactions to give substantial asymmetric induction with these novel rhodium carboxylates.

While the majority of the α-diazocarbonyl compounds explored in this work were α-diazoketones, a number of α-diazoesters are also described. Details of chiral stationary phase HPLC analysis, single crystal analysis and 2D NMR experiments are included in the Appendix (*Appendix III-V*).

Contents

Declaration by Candidate

I declare that this thesis contains my own work and has not been submitted for another degree, either at University College Cork, or elsewhere

Brian Feerick

It may be that the gulfs will wash us down:
It may be that we shall touch the Happy isles,
And tho' we are not now that strength which in old days,
Moved earth and heaven; that which we are, we are;
One equal temper of heroic hearts,
Made weak by time and fate, but strong in will
To strive, to seek, to find, and not to yield.

Alfred, Lord Tennyson 'Ulysses'

This guy's walking down the street when he falls in a hole. The walls are so steep he can't get out.
"A doctor passes by and the guy shouts up, 'Hey you. Can you help me out?' The doctor writes a prescription, throws it down in the hole and moves on.
"Then a priest comes along and the guy shouts up, 'Father, I'm down in this hole can you help me out?' The priest writes out a prayer, throws it down in the hole and moves on.
"Then a friend walks by, 'Hey, Joe, it's me can you help me out?' And the friend jumps in the hole. Our guy says, 'Are you stupid? Now we're both down here.' The friend says, 'Yeah, but I've been down here before and I know the way out.'"

Chief of Staff Leo McGarry, The West Wing

To Mum and Dad

Chapter 1

Introduction

Facts are stubborn things; and whatever may be our wishes, our inclinations, or the dictates of our passion, they cannot alter the state of facts and evidence.

John Adams, Second President of the United States (1735-1826)

If it looks like a duck, and quacks like a duck, we have to at least consider the possibility that we have a small aquatic bird of the family anatidae on our hands.

Douglas Adams

Contents

1.1 Introduction

Following the initial reports by Curtius in 1883,[1] the diazo moiety has emerged as a versatile building block to effect carbon-carbon bond formation *via* thermolysis, photolysis and transition metal catalysis. Transition metal-catalysed reactions of α-diazocarbonyl compounds lead to the generation of metallocarbenoids; these electrophilic complexes undergo a broad spectrum of synthetic transformations often featuring highly efficient chemo-, regio-, and stereoselectivity, unlike the analogous indiscriminate free carbenes. Several extensive reviews have been published highlighting the utility of α-diazocarbonyl compounds in the realm of organic synthesis.[2-11] A summary of the main reaction pathways of metallocarbenoids is shown below (**Figure 1.1**).

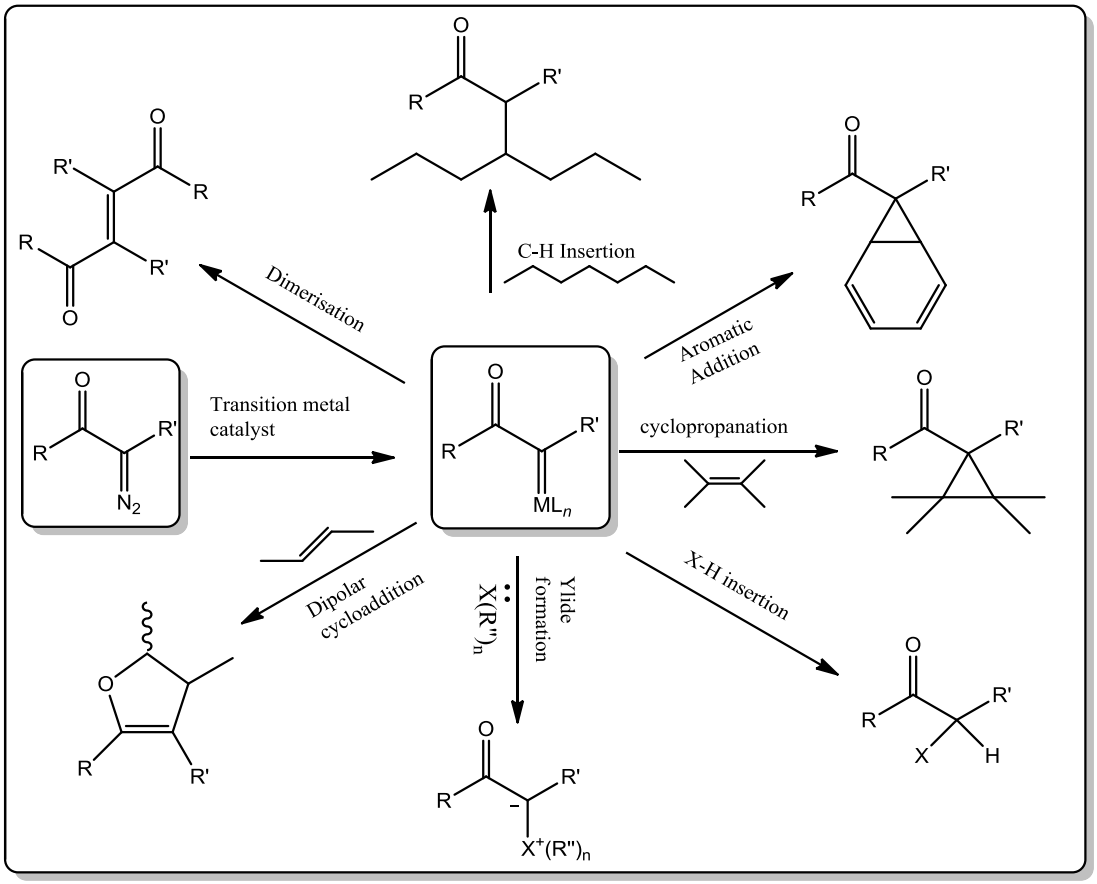


Figure 1.1: Transformations of metallocarbenoids

Synthetic approaches employing metallocarbenoids derived from diazo compounds are prevalent in organic chemistry with noteworthy examples including inter- and intramolecular cyclopropanation, C–H insertion, aromatic addition, 1,3-dipolar cycloaddition and ylide formation/rearrangements.

This chapter will entail an overview of established and recently developed methods for the preparation of α-diazocarbonyl compounds. It will then focus on the reactivity of various α-diazocarbonyl systems, as well as the mechanism for their transformations in the presence of transition metal catalysts. Finally, examples of heterocyclic α-diazocarbonyl compounds and their subsequent transition metal-catalysed pathways will be discussed.

1.2 Preparation of α-diazocarbonyl compounds

α-Diazocarbonyl compounds constitute a class of compounds with wide-ranging synthetic impact, allowing rapid generation of a diverse array of compounds. α-Diazocarbonyl compounds can be prepared by two principal routes; acylation of diazoalkanes and diazo transfer (**Figure 1.2**).

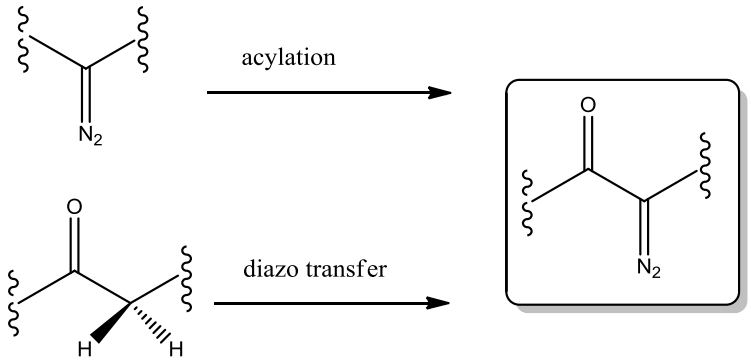
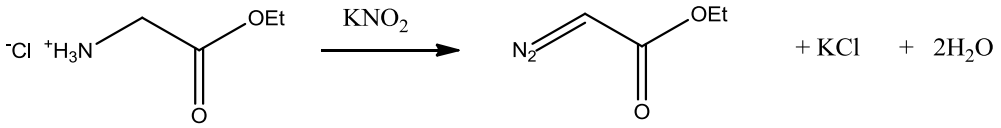


Figure 1.2: Two principal routes to prepare α-diazoketones

The first synthesis of α-diazocarbonyl compounds was accredited to Curtius in 1883.[1] In that work, a series of diazotisation reactions were carried out on the esters of natural α-amino acids (**Scheme 1.1**). The initial efforts involved reaction of glycine hydrochloride **1** with potsssium nitrite to generate ethyl diazoacetate **2**.



1 **2**

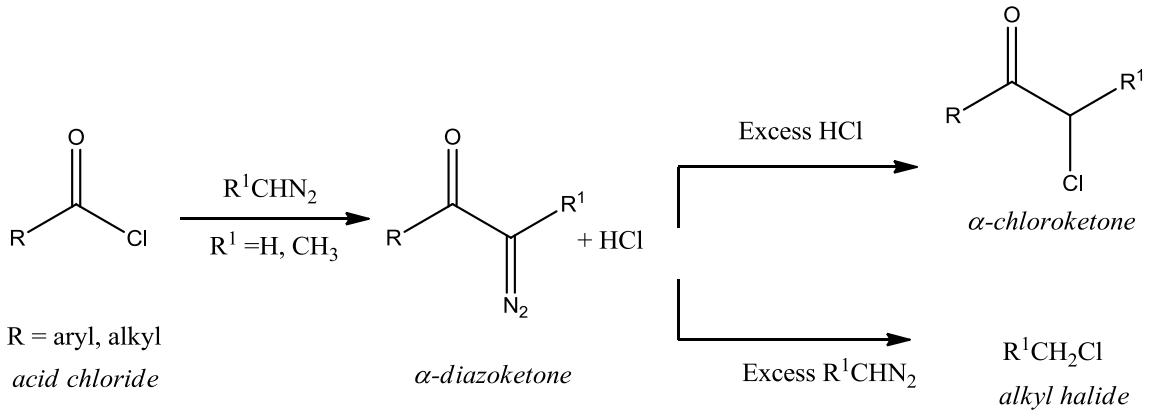
Scheme 1.1

1.2.1 Acylation of diazoalkanes

The acylation of diazoalkanes is usually achieved by reaction with acid chlorides or unsymmetrical anhydrides. The reactive intermediates are prepared from the parent carboxylic acid prior to the acylation. This strategy remains a prominent route to α-diazoketones, however, in the scenario where the requisite acid chloride or anhydride is not easy to prepare, *e.g.* heterocyclic acid chlorides, alternative synthetic approaches have to be applied. A summary of existing methodologies, new developments in the preparation, and *in situ* generation of α-diazocarbonyl compounds will be described.

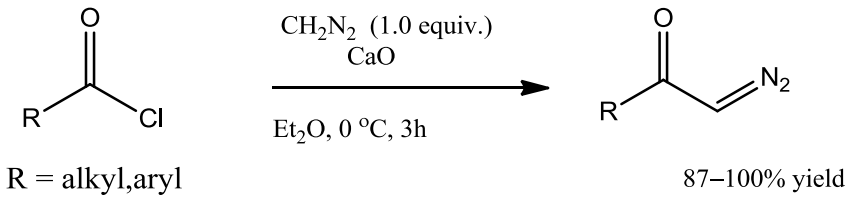
1.2.1.1 Arndt-Eistert synthesis of α-diazoketones

Seminal work by Arndt and Eistert,[12] supplemented thereafter by Bradley and Robinson,[13] first demonstrated that α-diazoketones could be prepared using slow addition of an acid chloride to a solution containing an excess of diazomethane (**Scheme 1.2**). Generation of the unwanted α-chloroketone can be minimised through the use of an excess of diazomethane in the reaction. Ocassionally, lutidine or another sacrificial base such as triethylamine may be added to the reaction, which also serves to scavenge excess hydrogen chloride. The Arndt-Eistert procedure is the most widely used methodology for the preparation of terminal and internal α-diazoketones. Further unsymmetrical α-diazoketones are synthesised by replacing diazomethane with diazoethane or higher diazoalkane homologues in the acylation. Introduction of trimethylsilyldiazomethane ($TMSCHN_2$) by Seyferth in 1968 reflected a development of the standard diazoalkane acylation avoiding the use of diazomethane,[14] although this has mainly been utilised in the conversion of carboxylic acids to the corresponding methyl esters.[14-16] It is only in more recent times that $TMSCHN_2$ has been applied to the preparation of terminal α-diazoketones using acid chlorides.[17,18]



Scheme 1.2: Side products from acylation

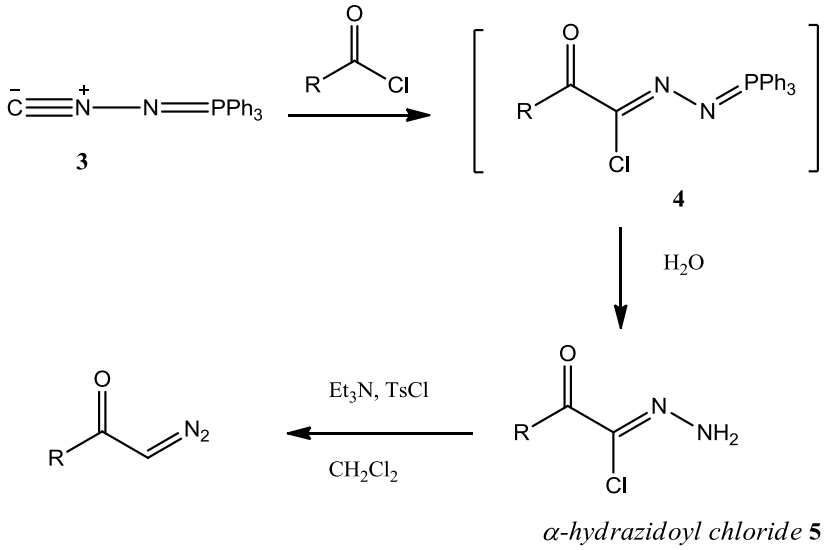
In a 2010 report, Kimpe and co-workers proffered a modification of the Arndt-Eistert synthesis of α-diazoketones, requiring minimal diazomethane in the presence of calcium oxide (**Scheme 1.3**).[19] The calcium oxide scavenges any hydrogen chloride generated, enabling the clean formation of α-diazoketones in high yields. An advantage of this method is the possibility of reducing the amount of diazomethane required, thereby providing safer applications for large-scale processes.



Scheme 1.3

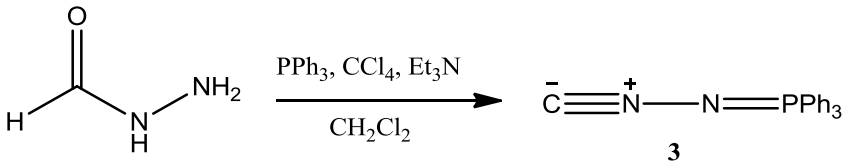
1.2.1.2 Formation of α-diazoketones from acid chlorides and *N*-isocyanoiminotriphenylphosphorane

In 2000, Aller and co-workers devised a useful alternative to using diazomethane in the formation of α-diazoketones (**Scheme 1.4**).[20] This method involves *N*-isocyanoiminotriphenylphosphorane **3**, which reacts with an acid chloride to form an intermediate addition product **4**. The intermediate product **4** is hydrolysed to afford precursor α-ketohydrazidoyl chloride **5** and subsequently treated with triethylamine and a catalytic amount of toluenesulfonyl chloride to furnish the α-diazoketones in high yields. Isolation of the purified α-diazoketones using this methodology is considered to be more straightforward, cleaner and higher yielding than those involving diazomethane (CH_2N_2) or the commercially available alternative trimethylsilyldiazomethane ($TMSCHN_2$).



Scheme 1.4

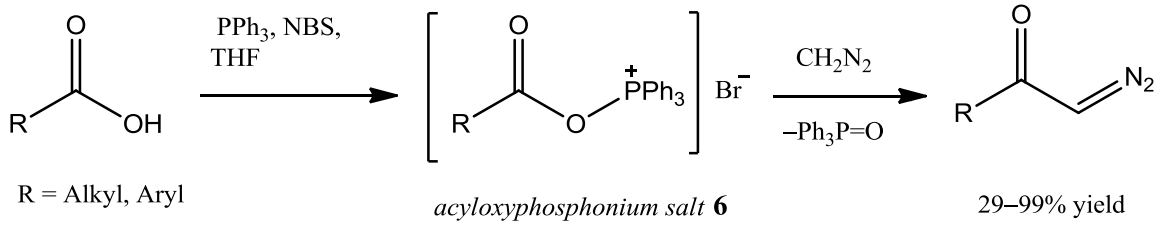
Later studies by Bio disclosed an improvement of Aller's procedure with formation of the *N*-isoacyliminotriphenylphosphorane **3** from formic hydrazide (**Scheme 1.5**).[21] This two-step protocol provided higher yields of α-diazoketones from precursor carboxylic acids than either diazomethane or trimethylsilyldiazomethane. The author acknowledges that atom economy is not particularly efficient in preparing α-diazoketones using this method due to use of *N*-isoacyliminophosphorane **3** and given that the overall reaction is multistep. However, given the safety concerns associated with diazomethane and the formation of side products, namely α-chloroketone and the α-TMS ketone while employing $TMSCHN_2$, this can be viewed as a safe and practical alternative for large-scale syntheses of α-diazocarbonyl compounds.



Scheme 1.5

1.2.1.3 Synthesis of α-diazoketones using PPh_3/NBS

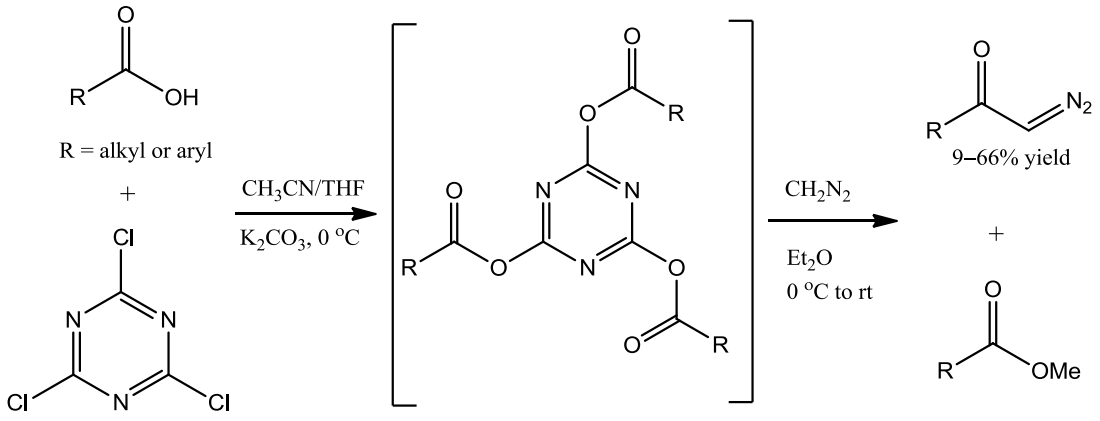
In an effort to activate carboxylic acids under mild conditions, Cuevas-Yañez and co-workers developed methodology involving triphenylphosphine and *N*-bromosuccinimide (**Scheme 1.6**).[22] This synthesis involved addition of *N*-bromosuccinimide to triphenylphosphine and an appropriate acid to generate an acyloxyphosphonium salt **6**, which subsequently reacts with diazomethane to afford α-diazoketones. The reaction conditions reported are mild and compatible with a diverse range of functional groups.



Scheme 1.6

1.2.1.4 Formation of α-diazoketones using cyanuric chloride and diazomethane

An alternative approach to prepare α-diazocarbonyl compounds has been reported by Forbes, this involved the use of cyanuric chloride as a promoter, the specific carboxylic acid and diazomethane (**Scheme 1.7**).[23] A variety of aryl carboxylic acids and aliphatic carboxylic acids were used as substrates in this work. The α-diazoketones were obtained in moderate to good yields with the corresponding methyl ester also observed in significant amounts, the ester presumably originating from reaction of the acid with diazomethane. The author claims some of the benefits of this route are that water does not have to be stringently removed in the reaction and the procedure is carried out in one-pot.



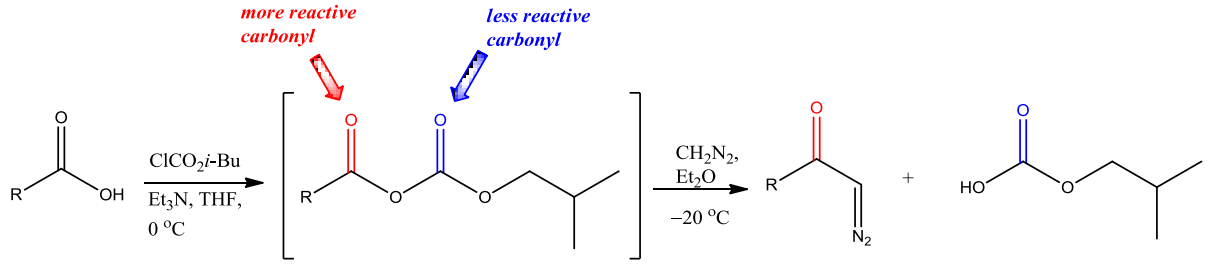
Scheme 1.7

Using this protocol, two key trends were identified; aryl carboxylic acids were found to be more suitable substrates than aliphatic carboxylic acids and moderately electron-deficient aryl carboxylic acids were significantly better candidates than their electron-rich aryl counterparts. Advantages of this technique include the use of non-toxic and non-expensive reagents as well as formation of non-toxic and easily removed side-product, namely the insoluble hydroxytriazine. However, this methodology presents a drawback due to its limited applicability to aromatic carboxylic acids and appreciable formation of undesired methyl

ester. Use of other diazoalkanes in place of diazomethane has yet to be attempted using this methodology and should be investigated to ascertain the scope of this procedure.

1.2.1.5 Unsymmetrical anhydrides and DCC-mediated coupling

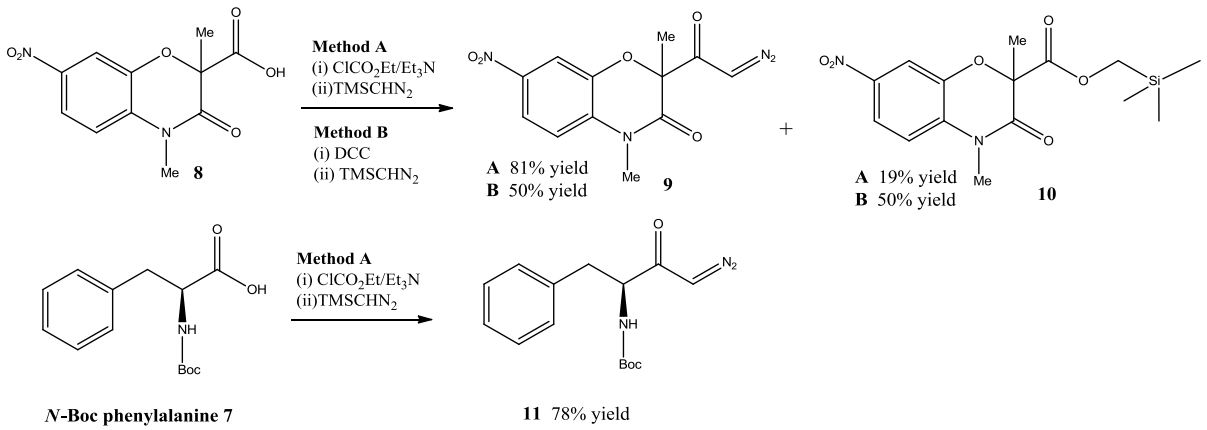
Unsymmetrical anhydrides and *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling reagents can be used as alternative procedures to prepare α-diazoketones where the formation of acid chlorides is impeded due to presence of other reactive functionalities in the substrate. In the anhydride protocol, the carboxylic acid is activated and the ensuing unsymmetrical anhydride can react with the diazoalkane at either of the two carbonyl moieties. In the two potential reaction sites, one carbonyl group is bordered by one oxygen atom, while the other is flanked by two. This disparity in reactivity directs the diazoalkane acylation to the carbonyl originating from the carboxylic acid to afford the α-diazoketone (**Scheme 1.8**). Conveniently, no hydrogen chloride is generated and therefore less diazoalkane is required in the unsymmetrical anhydride approach.



Scheme 1.8

Nicolaou and co-workers disclosed a mild one-pot protocol for the generation of hindered α-diazoketones using acyl mesylate methodology.[24] A range of sterically impeded α-diazoketones were synthesised using this procedure while in certain cases formation of the analogous methyl ester was observed, although through use of acetonitrile as solvent generation of this side product could be diminished.

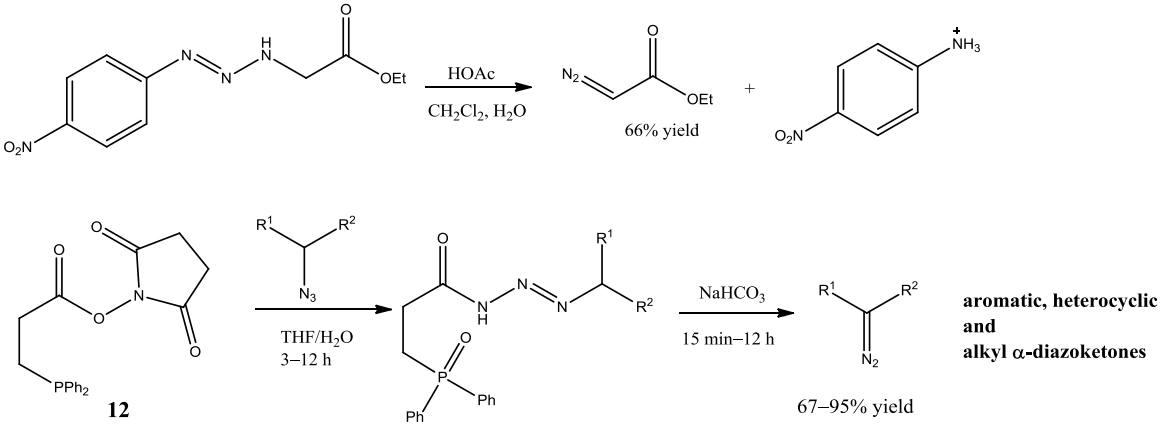
Building on the original report by Tarbell in 1957,[25] Dolenc *et al.* have employed unsymmetrical mixed anhydrides in the synthesis of α-diazoketones using Boc-phenylalanine **7** and 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-carboxylic acid **8** as substrates (**Scheme 1.9**).[26] In contrast to classical approaches, $TMSCHN_2$ was used in place of diazomethane for the acylation. Both the DCC-mediated coupling and unsymmetrical anhydride methodologies were applied to prepare the α-diazoketone **9**, with higher isolated yields observed for mixed anhydride/$TMSCHN_2$ compared to the DCC/$TMSCHN_2$ combination. In the preparation of **9**, the unsymmetrical anhydride method afforded the α-diazoketone in 81% yield, whereas the DCC method only gave a 50 : 50 mixture of α-diazoketone **9** and trimethylsilyl ester **10**. Reaction of Boc-phenylalanine **7** with ethyl chloroformate afforded the α-diazoketone **11** in 78% yield, although this not attempted using Method B. The yields for the syntheses *via* mixed anhydride/$TMSCHN_2$ were comparable with conventional procedures.



Scheme 1.9

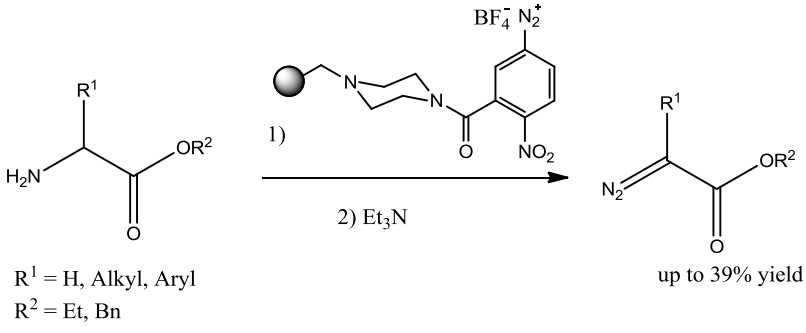
1.2.1.6 Formation of diazo compounds *in situ* from triazenes and diazonomium salts

It has been demonstrated that triazenes can function as suitable precursors to α-diazocarbonyl compounds. Treatment with acid or base induces fragmentation, thereby generating an α-diazocarboxylic ester and an aromatic amine (**Scheme 1.10**). However, due to a limited substrate scope the potential of this technique has remained unfulfilled. A related modification developed by Myers and Raines involves a phosphine-mediated conversion of organoazides *via* acyltriazene into a broad range of α-diazocarbonyl compounds.[27] The phosphine reagent has been adapted with a succinimidyl-based model **12** proving the most successful as it effectively suppresses the competing Staudinger reaction.



Scheme 1.10

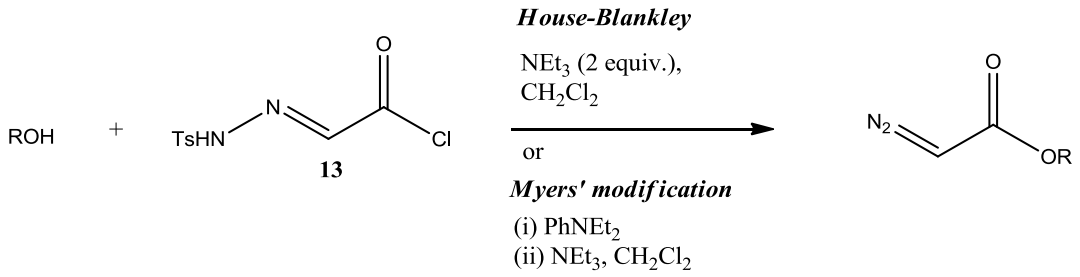
Polymer-bound diazonium salts have been successfully used by Bräse and Schroen to synthesise α-diazoacetates through coupling with α-amino esters under basic conditions (**Scheme 1.11**),[28] though only moderate yields were obtained for this process.



Scheme 1.11

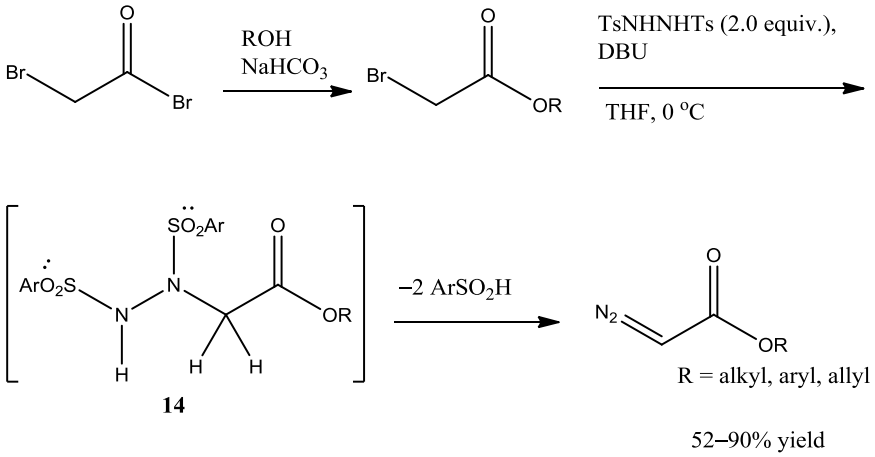
1.2.1.7 Diazoacetylation of Alcohols

α-Diazoacetates are generally accessible by two principal routes; diazo transfer followed by deacylation under basic conditions as carried out by Regitz[29] or by reaction of an alcohol with the *p*-tosylsulfonylhydrazone of glyoxylic acid chloride **13**, first investigated by House and Blankley in 1968 (**Scheme 1.12**).[30] The activated carboxylic acid derivative **13** has proved a successful strategy to synthesise α-diazoesters from various alcohol substrates with the eponymous reagent becoming the conventional method for formation of α-diazoacetates. A modification of this method by Corey and Myers involving the introduction of *N*,*N*-diethylaniline has further enhanced the efficiency of this reaction.[31]



Scheme 1.12

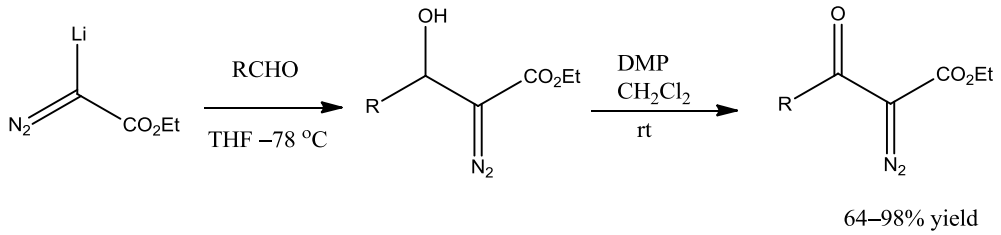
More recently, Fukuyama and co-workers described a novel synthetic method for the preparation of α-diazoacetates from the corresponding α-bromoacetyl bromide in a simple two-step process. (**Scheme 1.13**).[32] The process involves initial formation of α-bromoacetate, from the alcohol and bromoacetyl bromide followed by treatment with *N*,*N′*-ditosylhydrazine and DBU. An interesting note on this mechanism is that it involves a facile two-fold elimination of toluenesulfinic acid from the initial α-hydrazineacetic ester **14**. Numerous alcohol substrates are compatible with this procedure such as primary and secondary, saturated and unsaturated alcohols.



Scheme 1.13

1.2.1.8 Use of ethyl lithiumdiazoacetate to form α-diazo-β-ketoesters

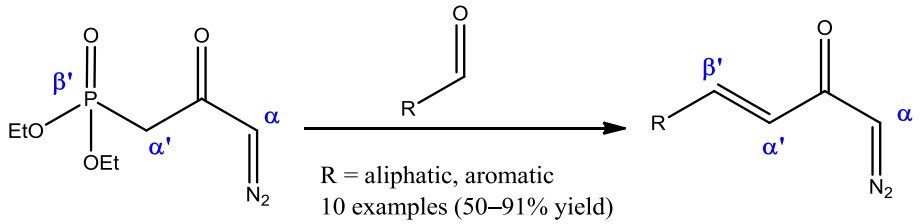
The first preparation of α-diazo-β-ketoesters from their corresponding α-diazo-β-hydroxyesters *via* mild and selective oxidation was described by Weinreb using Dess-Martin periodinane (DMP) and pyridine (**Scheme 1.14**).[33] The α-diazo-β-hydroxyesters were generated from a diverse range of aliphatic, aromatic, heterocyclic and unsaturated aldehydes by reaction with lithiated ethyl diazoacetate in tetrahydrofuran. The formation of these α-diazo-β-ketoesters could also be achieved by traditional diazo transfer chemistry involving a suitable β-ketoester but this route obviates the use of potentially explosive diazo transfer reagents. The acylating reagent is prepared from lithiation of the commercial ethyl diazoacetate **2**, which is also potentially explosive. A one-pot preparation of α-diazo-β-ketoesters from aldehydes using ethyl diazoacetate, 2-iodoxybenzoic acid (IBX) and DBU has been reported by Steel and co-workers in high yields,[34] although use of explosive IBX also raises safety concerns.



Scheme 1.14

1.2.1.9 Formation of α',β'-unsaturated α-diazoketones using a Horner-Wadsworth-Emmons reaction

Burtoloso and co-workers have developed a new route to α',β'-unsaturated α-diazoketones through the use of an α-diazo-β'-phosphonate **15**, derived from commercially available 2-(diethoxyphosphoryl)acetic acid (**Scheme 1.15**).[35] After an initial optimisation process, diazophosphonate **15** was reacted with an array of aldehydes using sodium hydride as base in THF at −78 °C. The desired α-diazocarbonyl systems were formed in high yields from branched, unbranched, aromatic and amino substituted aldehydes.



15

Scheme 1.15

1.2.2 Diazo transfer

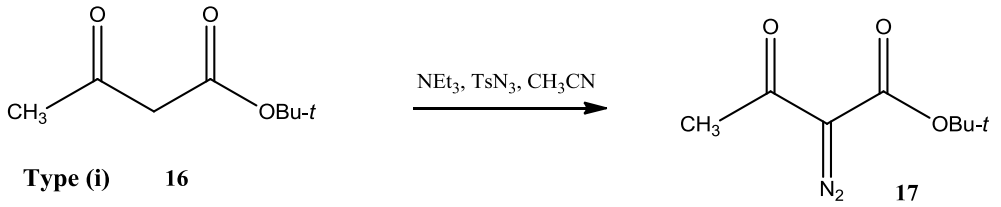
While acylation is a useful technique for generating diazo compounds, its overall effectiveness has been hindered by the difficulty in preparing cyclic α-diazoketones. In 1910,[36] Dimroth first introduced diazo transfer methodology and the technique was further developed and refined by Regitz in 1964,[37-40] providing a reliable and efficient general route to α-diazoketones incorporating both cyclic and acyclic substrates. This has proved an efficient strategy in the formation of cyclic α-diazoketones, the synthesis of which had previously been challenging, as well as facilitating an expansion of the breadth of α-diazocarbonyl compounds which can be readily accessed.[41]

1.2.2.1 Diazo transfer reactions

The diazo transfer methodology usually consists of reaction of an arylsulfonyl azide with the precursor containing an acidic carbon adjacent to a carbonyl group or other electron-withdrawing group. The method requires an appropriate base of sufficient strength to deprotonate the substrate. The range of accessible substrates can be grouped according to the ease with which the carbon can be activated for the diazo transfer [type (i) and type (ii)], which is determined by the acidity of the internal active methylene group.

A type (i) substrate possesses an internal active methylene adjacent to the carbonyl group and/or other electron-withdrawing group which is sufficiently acidic to be deprotonated by the base and hence undergo diazo transfer easily. Examples of compounds where the internal active α-methylene group is flanked by two activating groups include malonic esters, β-ketoesters, β-ketoamides, β-ketophosphonates, β-ketosulfones and β-diketones. Charette and co-workers have also prepared α-cyano-, α-nitro- and α-phenylsulfonyl-α-diazocarbonyls from precursors suitable for this methodology,[42,43] while Davies has highlighted the use of aryl-,[44,45] heteroaryl-[45] and vinylacetates[46] as further activated substrates for diazo transfer.

With regard to the diazo transfer technique, *p*-tosyl azide has been the most widely used reagent to effect diazo transfer following Regitz's seminal work in the 1960's.[37-40] In the example below (**Scheme 1.16**), reaction of β-dicarbonyl substrate **16** with *p*-tosyl azide in acetonitrile and triethylamine as base provided the α-diazo-β-ketoester **17**.[47] In 1990, Koskinen reported excellent yields (up to 96%) using diazo transfer under mildly basic conditions employing K_2CO_3/acetonitrile allied with *p*-tosyl azide for various type (i) substrates.[48]



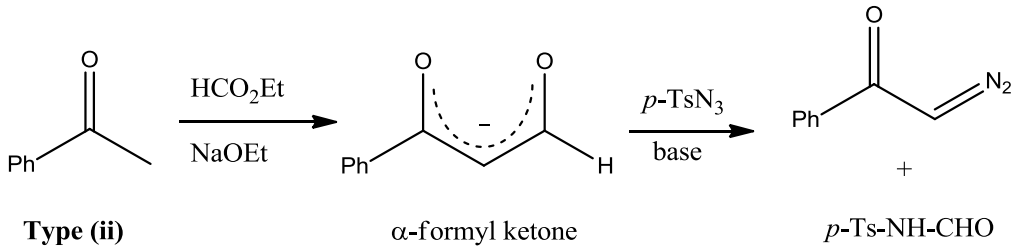
Type (i) **16** **17**

Scheme 1.16: Standard diazo transfer technique for type (i) substrates

In the case of simple acyclic ketones and esters where the methylene group is flanked by only one activating group, these are described as type (ii) substrates and are poor substrates for direct diazo transfer onto the enolisable ketones and carboxylic esters. In type (ii) compounds, the methylene group is not sufficiently activated and a different approach is needed. This can be accomplished through use of a stronger base in the enolisation or alternatively, these

substrates must first be activated by the appending of an additional electron-withdrawing group (EWG), which is eliminated following diazo transfer to the temporarily activated methylene group.

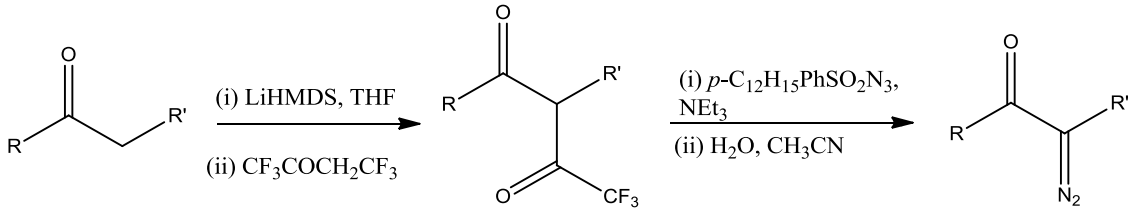
Accordingly, Regitz and co-workers developed their "deformylating diazo group transfer" strategy in 1967.[29,49] This involves temporary introduction of an additional activating group, typically a formyl group, by Claisen condensation of the simple ketone enolate with ethyl formate. Diazo transfer to the methylene group of the activated β-dicarbonyl is swiftly followed by loss of the formyl group to afford the α-diazocarbonyl product and sulfonyl formamide side product (**Scheme 1.17**).



Scheme 1.17: Regitz's "deformylating diazo transfer" technique for type (ii) substrates

Numerous cyclic and acyclic α-diazoketones and α-diazoesters, whose formation had previously proven difficult and/or low-yielding, have been prepared using Regitz's deformylating methodology. Other advantages using this methodology include formation of the α-diazocarbonyl compound without isolation of the α-formyl ketone intermediate.

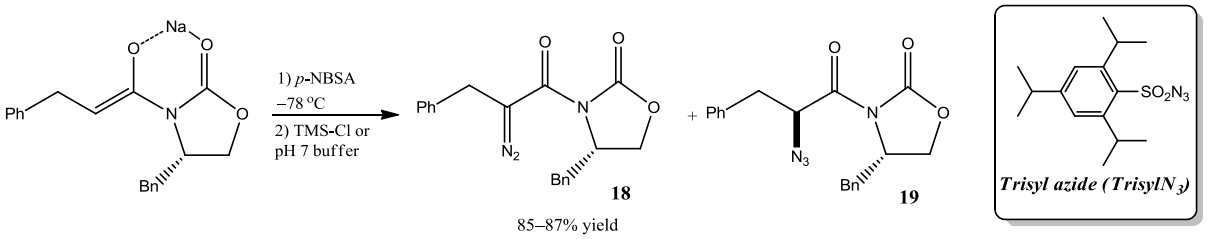
A more general and even more efficient activation method was established by Danheiser and co-workers in 1990,[50] with this adaptation enabling the construction of α-diazoketones from problematic substrates such as base-sensitive α,β-enones and heteroaryl ketones. The Clasien formylation step is replaced by a trifluoroacetylation step (reaction of the enolisable carbonyl compound with LiHMDS/$CF_3CO_2CH_2CF_3$) and use of mesyl azide as diazo transfer reagent, which was superceded in later work by the more stable 4-dodecylbenzenesulfonyl azide.[51] An example of this approach is shown below (**Scheme 1.18**).



61–95% yield

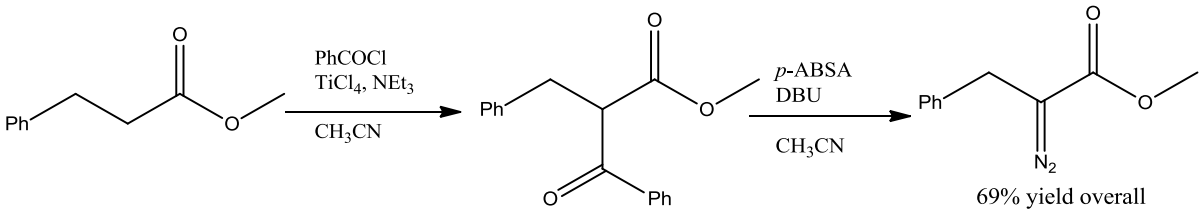
Scheme 1.18: Danheiser's "detrifluoroacetylative diazo transfer" strategy[51]

In 1990, Evans and co-workers applied an imide enolate strategy to effect azide transfer to chiral oxazolidinones. Interestingly, use of *para*-nitrobenzenesulfonyl azide (*p*-NBSA) as the diazo transfer reagent and sodium *bis*(trimethylsilyl) amide (NaHMDS) afforded the unexpected α-diazoketone **18** in preference to the desired azide **19** (**Scheme 1.19**).[52] The α-diazoketone was formed in high yield using this process, providing access to asymmetric cyclisations. In addition, use of *p*-TsN_3 and *p*-Trisyl azide (*p*-TrisylN_3) in place of *p*-NBSA resulted in predominant generation of **19** using the former and complete elimination of α-diazoketone **18** formation employing the latter.



Scheme 1.19

Taber *et al*. have demonstrated a simple and inexpensive diazo transfer technique through $TiCl_4$-mediated reaction of a suitable ester with benzoyl chloride (**Scheme 1.20**).[53] The resultant benzoylated ester undergoes debenzoylation diazo transfer affording the α-diazocarboxylates in good yield.



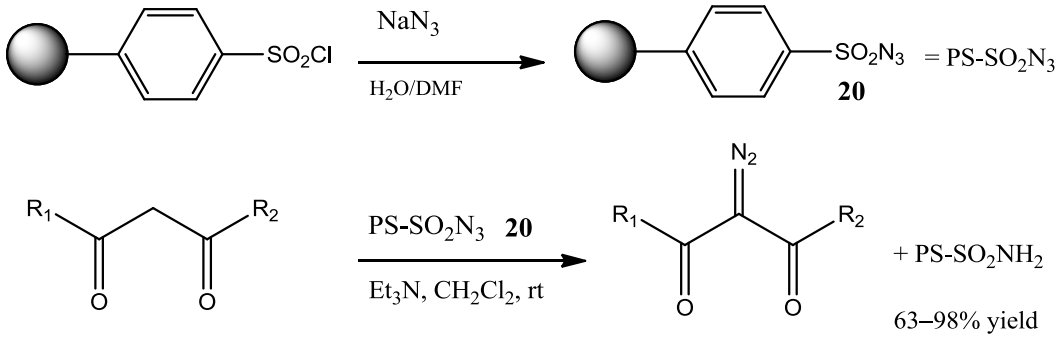
Scheme 1.20

More recently, diazo group transfer reactions in ionic liquids, which are based on 1-butyl-3-methylimidazolium (bmim) salts, have been reported by Ramachary.[54] Modern alternatives to Regitz's procedure have succeeded in making the synthesis of the α-diazocarbonyl compounds from type (ii) substrates possible under diverse reaction conditions in an effective and economic manner.

1.2.2.2 New developments in diazo transfer reagents

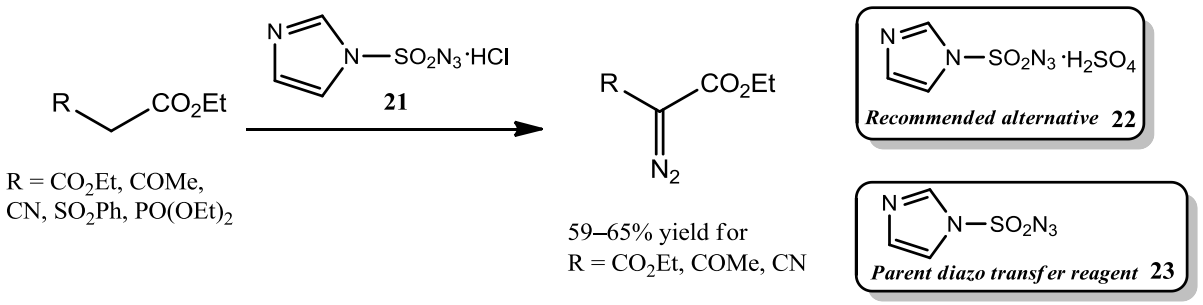
Since the inception of efficient diazo transfter methodology in the early 1960's,[37-40] *p*-tosyl azide has been the favored reagent for the preparation of α-diazocarbonyl compounds using this protocol. However, various drawbacks for this reagent have been recognised, including difficulty in chromatographic separation of the sulfonamide byproduct from the diazo component.[55] Other caveats include its high impact sensitivity and low initiation temperature, which contribute to make it potentially explosive,[56] therefore, the development of alternatives to effect diazo transfer merits significant investigation. The alternative reagents aim to satisfy the dual criteria that the azide is a) less likely to explode than *p*-tosyl azide, and b) transformed (during the reaction) into a sulfonamide derivative that can be separated from the diazo compound more conveniently and efficiently than the corresponding *p*-tosyl amide.[4]

In 2001, polystyrene-supported benzenesulfonyl azide **20** was proposed as a safe-to-handle diazo transfer reagent (**Scheme 1.21**),[57] offering product isolation by resin filtration thus affording the α-diazocarbonyl compounds in good to excellent yields without the necessity of an aqueous workup.



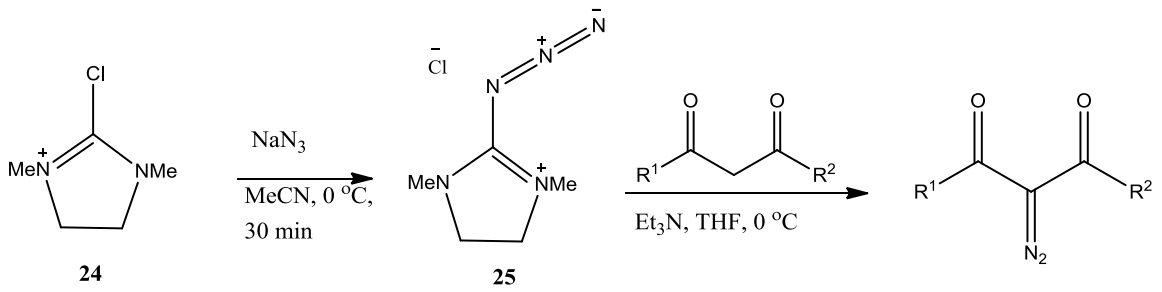
Scheme 1.21

Imidazole-1-sulfonyl azide hydrochloride **21** is a recently-developed crystalline diazo transfer reagent with potential benefits of an easy preparation as well as having a long shelf-life.[58] Effective diazo transfer has been achieved for malonic esters, β-ketoesters and cyanoacetates, however; diazo transfer using this reagent **21** was unsuccessful for both phenylsulfonylacetates and diethoxyphosphorylacetates (**Scheme 1.22**). The same reagent has also been utilised in the synthesis of azides from primary amines in work by the same author. However, subsequent work by Goddard-Borger has shown this compound to be impact sensitive, prompting a search to identify a safer alternative with respect to heat, impact, friction and electrostatic discharge.[59] Following an extensive screening process, imidazole-1-sulfonyl azide·H_2SO_4 salt **22** was the recommended alternative with other advantages including ease of preparation, inexpensive starting materials and long-shelf life provided there is exclusion of moisture. Even more recent efforts by Hui have reported preparation of the parent imidazole-1-sulfonyl azide **23** *via* facile two-step process from shelf-stable sulfuryl diimidazole precursor.[60] Significant advantages to this protocol involve generation of the diazo transfer reagent without requiring purification, thereby minimising potential formation of explosive hydrazoic acid (HN_3) or sulfuryl diazide ($N_3SO_2N_3$) which enables large-scale preparation of the diazo transfer reagent (~100 g).



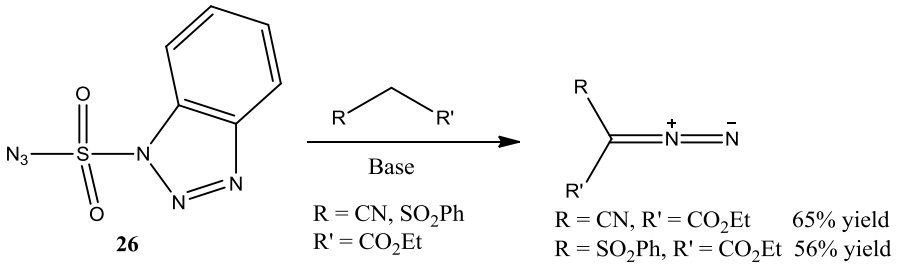
Scheme 1.22

Okauchi and co-workers have designed an azidoimidazolium salt **24** (guanidine diazonium salt) to mediate diazo transfer reactions.[61] The diazo transfer reagent was prepared by the reaction of commercially available chloroimidazolium salt **25** with sodium azide (**Scheme 1.23**). On examining the scope and limitations of this method, a series of 1,3-dicarbonyl compounds were subjected to diazo transfer conditions; the corresponding 2-diazo-1,3-dicarbonyl compounds were easily isolated and obtained in excellent yields. The ketoamides and diesters required a longer reaction time but were still obtained in high yields. Cyclic 1,3-dicarbonyl compounds were also synthesised using this method.



Scheme 1.23

Katritzky has highlighted the use of a new heterocyclic diazo transfer reagent, benzotriazol-1-yl-sulfonyl azide ($BtSO_2N_3$) **26**.[62] The compound **26** is a crystalline, stable and easily available diazo transfer reagent which has been used for N-, O-, C- and S-acylations, as well as the formation of α-diazocarbonyl compounds (**Scheme 1.24**). This reagent can be readily prepared by reacting chlorosulfonyl azide, prepared *in situ* from sodium azide and sulfuryl chloride, with 1*H*-benzotriazole and pyridine in methanol to provide **26**.



Scheme 1.24

However, an explosion has been reported for this diazo transfer reagent through an inadvertent acidic workup, possibly generating the highly explosive hydrazoic acid (HN_3) by reaction of the acid with residual azide.[63] This illustrates that there is still an inherent risk associated with diazo transfer reagents and sufficient safety measures must be adhered to at all times when handling these reagents.[64]

1.3 Reactivity of diazo compounds

The various types of diazo compounds exhibit differing scope in their reactivity towards transformation of the parent diazo substrate to the highly reactive carbene or carbenoid complex. Intuitively, one would place the highly explosive and unstable diazoalkanes *(i.e.* diazomethane and diazoethane) as the most reactive diazo compounds. It is observed (**Figure 1.3**) that α-diazoketones are more reactive than corresponding α-diazoacetates (*e.g.* ethyl diazoacetate), which are in turn more reactive than analogous α-diazoacetamides.[10,65] It can be rationalised that compounds where the diazo moiety is adjoined by two carbonyl groups are more stable than those bordered by only one carbonyl group, due to enhanced inductive and resonance effects. This serves as a useful outline of the reactivity of various diazo compounds and a guide to the activity of the catalysts required in preparing the corresponding metallocarbenoids from these precursors. Factors which influence the effectiveness of the diazo transformation include the reactivity of the α-diazocarbonyl substrate, as well as the relative Lewis acidity of the catalyst employed.

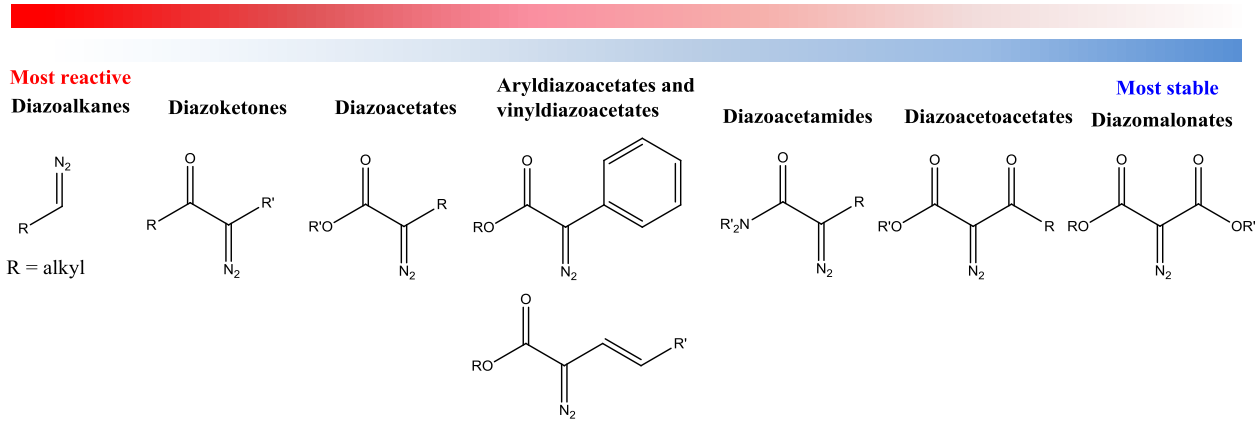


Figure 1.3: Scale of reactivity of diazo compounds

1.4 Mechanism of α-diazocarbonyl transformations with transition metal catalysts and discussion of catalysts

The accepted mechanism for the catalytic transformations of diazo compounds by transition metal catalysts was first postulated by Doyle in 1986.[66] The initial reaction involves electrophilic addition of the Lewis acid metal catalyst possessing open coordination sites at the metal centre to the diazo compound, triggering extrusion of dinitrogen from the intermediate ylide **27**. The loss of dinitrogen produces an electron-deficient metallocarbenoid **28**, which can react with an electron-rich substrate (S:) such as an alkene, aromatic ring, carbonyl, heteroatom or C–H bond, resulting in regeneration of the transition metal complex and completion of the catalytic cycle (**Figure 1.4**). Nitrogen is irreversibly extruded in what is observed to be the rate-determining step (RDS) for the process.[67] Kinetic studies reported by Alonso and Pirrung have provided some support for this mechanism.[68-71]

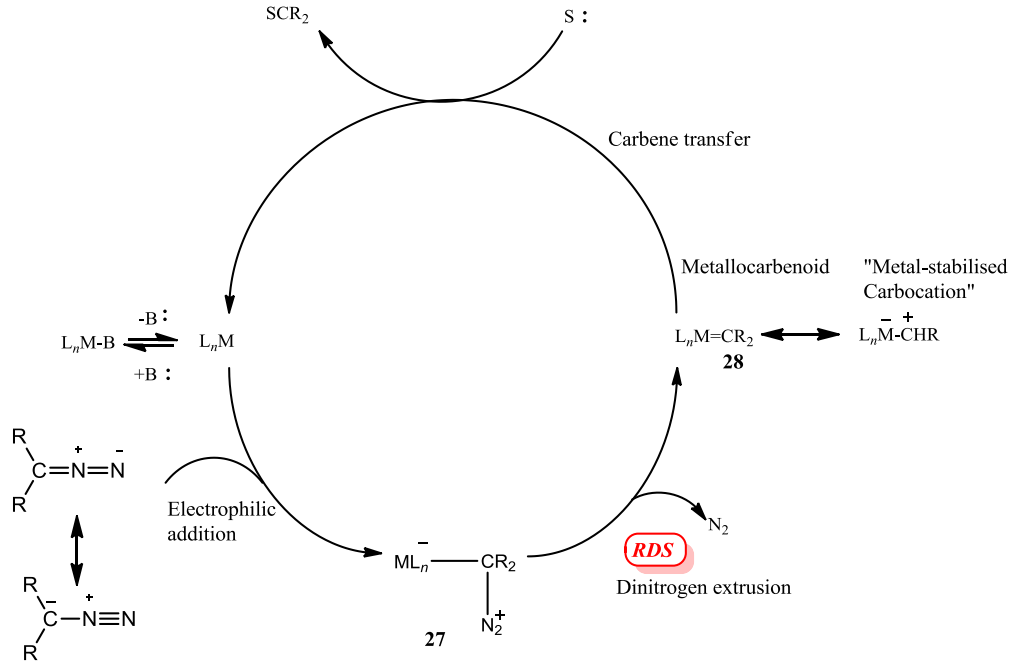


Figure 1.4: Doyle's proposed mechanism for metal carbene formation[66]

The early 1970's witnessed a shift in the landscape of transition metal-catalysed reactions of diazo compounds as rhodium(II) carboxylates **29** (**Figure 1.5**) were realised as proficient catalysts for these transformations.[68,72-78] The pioneering work of Teyssié and co-workers displayed that many of the reactions that were previously low-yielding using copper catalysis were found to proceed with greater efficiency and selectivity using rhodium(II) catalysis. Significant advancements, both in substrate scope and catalyst design arose in this burgeoning area following Teyssié's investigations, with numerous comprehensive reviews capturing the highlights in this field.[2-11,65,79-81]

The synthetic utility of these complexes can be enriched by modification of the archetypal $Rh_2(OAc)_4$ structure. Ligand replacement of the parent substrate leads to rhodium(II) carboxylates of type **29**. Further variants of these complexes include chiral proline-derived rhodium(II) carboxylates developed by McKervey[82] and Davies,[83-86] as well as rhodium(II) carboxylates bearing phthalimide[87-92] and tetrahydroquinoline[93] ligand scaffolds designed by Ikegami and Chiu respectively. The catalyst architecture can also be modified by convenient ligand replacement to generate rhodium(II) carboxamidates of general structure **30** first demonstrated by Bear[94-96] and more prominently employed in subsequent work by Doyle.[97] Ligand scope for the rhodium(II) carboxamidates includes proline, oxazolidine, imidazoline and azetidine functionalities. Moreover, the placement of the stereocentre contiguous to the carbene carbon is thought to be a key aspect of the high enantioinduction from these catalysts. In addition, enantiopure rhodium(II) phosphate catalysts **31** were also established by Pirrung[98] and McKervey[99] in the early 1990's. A more detailed discussion of rhodium(II) catalysts is found in Chapter 3 (see **Section 3.1**).

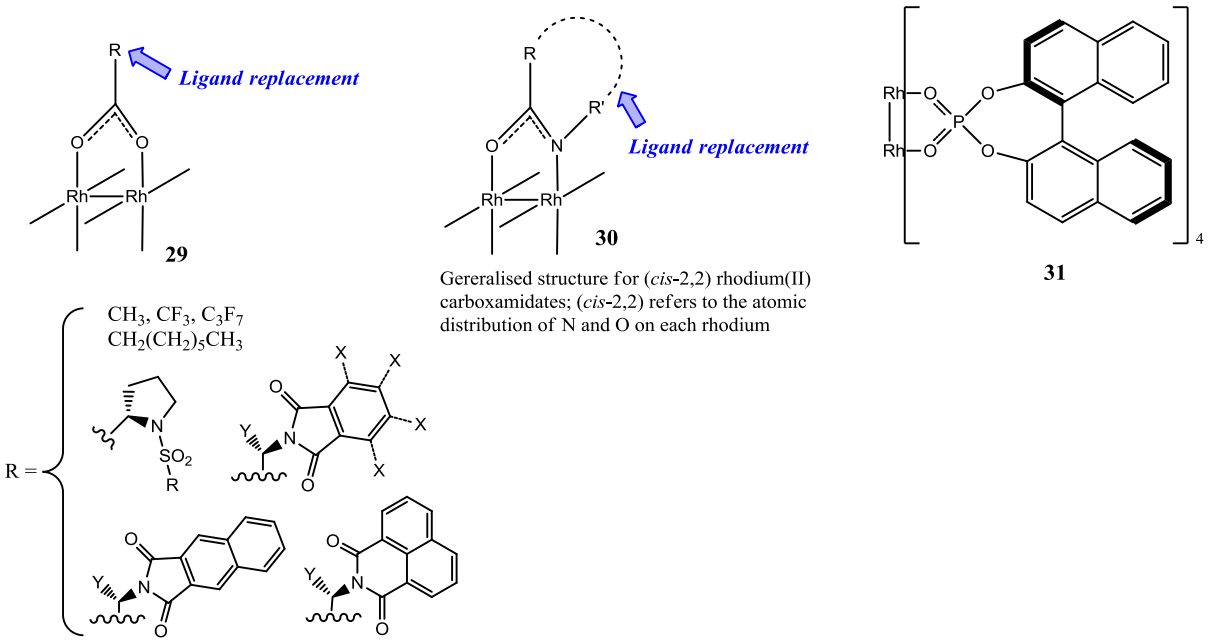


Figure 1.5: Generalised structures of rhodium(II) carboxylates, rhodium(II) carboxamidates and rhodium(II) phosphates

Work by Nozaki in the 1960's were the first examples utlising a copper-Schiff base system **32** for asymmetric induction, obtaining low enantioselectivities for intermolecular cyclopropanation involving styrene and ethyl diazoacetate.[100] This was soon surpassed following effective asymmetric cyclopropanation by Aratani and co-workers in 1975 obtaining high enantiopurity of 81% ee using a modified copper-Schiff base complex **33**.[101] This influential result led to resurgence in the use of copper catalysts in asymmetric synthesis. Further ligand design involved copper-semicorrin complexes **34** developed by Pfaltz in 1986,[102] as well as bis(oxazoline) ligands **35** (**Figure 1.6**) concurrently and independently established by the groups of Masamune,[103] Pfaltz[104] and Evans in 1990–91.[105]

Furthermore, the bis(oxazolines) provide multiple sites for further ligand diversification through alteration of the methylene bridge or replacement of the substituents on the heterocyclic backbone of the complexes, as illustrated for substrates **36** and **37** below (**Figure 1.6**). These catalysts systems permit tuning of the steric and electronic properties, which can be modified depending on the substitution of the bis(oxazoline) ligands, enabling highly enantiospecific reactions. The copper-bis(oxazoline) systems have found widespread use in asymmetric cyclopropanation reactions with the Evans ligand scaffold **38** proving particularly efficient affording excellent enantiopurities (97–99% ee) (**Figure 1.6**).[105] Maguire and co-workers have employed similar catalyst systems for use in intramolecular C–H insertion reactions, as well as aromatic cycloaddition reactions, providing enantioselectivities of up to 98% ee.[106-112] An extensive review of the advancements of copper catalysis in reactions with diazo compounds has been published by Zhang and Wang in 2012.[113]

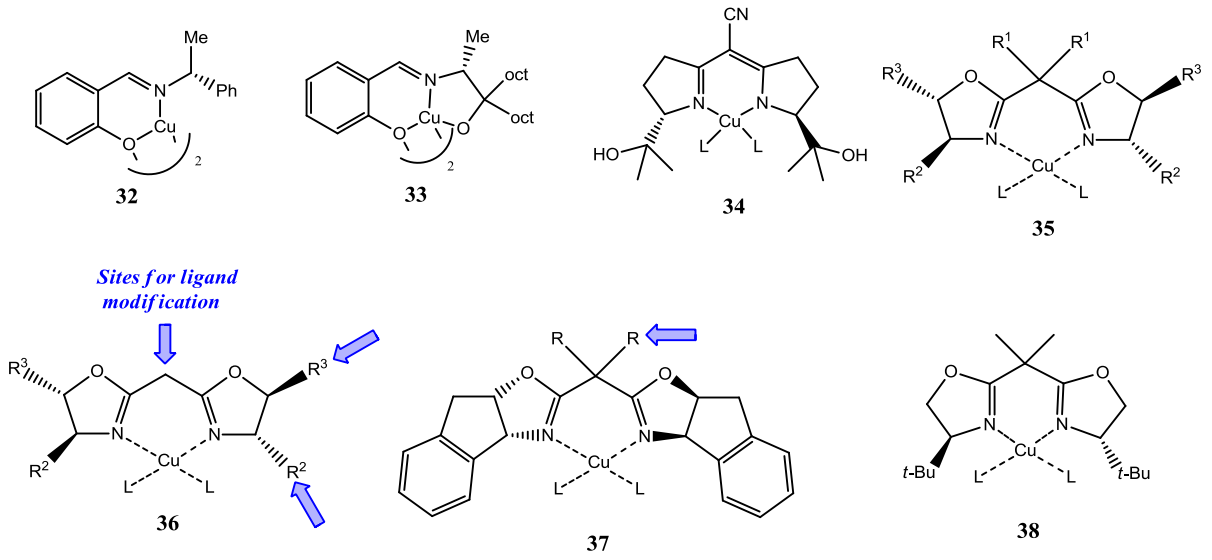


Figure 1.6: Copper-Schiff base complexes, copper-semicorrin complexes and copper-bis(oxazoline) complexes

The remainder of this chapter will focus on the transition metal-mediated transformations of α-diazocarbonyl compounds derived from heterocycles. In addition, synthetic modification of the products leading to the formation of polycyclic compounds, as well as natural and unnatural products has been employed.

1.5 Heterocyclic α-diazocarbonyl compounds as substrates in organic synthesis

1.5.1 Introduction

Heterocycles are abundant chemical entities making up about half of the known library of chemical compounds and display a ubiquitous chemical and biological significance. They play a central role in biochemical pathways due to their presence in DNA and RNA where the bases (cytosine, uracil, thymine, guanine and adenine) are all aromatic heterocycles.[114] Heterocyclic ring systems are found in a diverse range of compounds capable of eliciting biological responses, namely amino acids, co-factors, vitamins, hormones, antibiotics, alkaloids and pharmaceuticals,[115] which places them right at the core of the interface between chemistry, biology and medicine.

The following section is a comprehensive overview chronicling the reactions of heterocyclic α-diazocarbonyl substrates. This will focus primarily on X–H insertions, ylide formation/rearrangement, cyclopropanation, cycloadditions and examples of catalyst- and substituent-dependent chemoselectivity. Miscellaneous reactions of heterocyclic α-diazocarbonyl systems are also briefly discussed. The criterion for inclusion is that these compounds contain an α-diazocarbonyl group either attached to the heterocyclic ring directly or attached to a side-chain of the ring. Carbocyclic, acyclic and phenyl substrates are not addressed here.

1.5.2 X–H Insertion

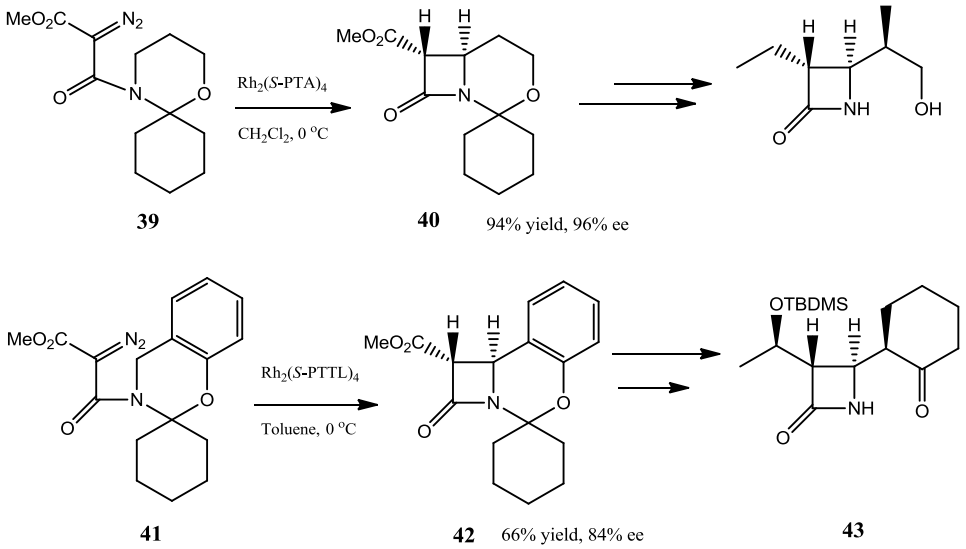
1.5.2.1 C–H insertion

Carbon–hydrogen insertion reactions represent an efficient route to assemble complex carbocyclic and heterocyclic systems *via* carbon-carbon bond formation using simple, readily synthesised precursors. A number of important reviews have appeared in recent years detailing the application of C–H insertions as a powerful synthetic strategy.[65,79,116-119] In 1981, Teyssié[75] published the first example of a successful insertion into a C–H bond in the presence of a rhodium(II) carboxylate catalyst, followed thereafter by the groups of Wenkert[120] and Taber.[121] Intermolecular and intramolecular C–H insertions have been utilised in the formation of carbocycles and heterocycles, with the intramolecular process proving particularly successful.

Taber and co-workers have reported that intramolecular C–H insertion reactions showed a high propensity for the formation of *trans* substituted cyclopentanone rings.[121] Another important aspect arising from this work was the preferential insertion into different C–H insertion sites, *eg.* tertiary, secondary and primary C–H bonds. From Taber's studies, the preferential order for C–H insertion illustrates methine insertion is more favoured than methylene insertion which in turn is appreciably more favoured than methyl insertion (CH > CH_2 >> CH_3). It is also noteworthy that allylic and benzylic C–H bond insertions are possible for aliphatic and aromatic systems, particularly in the cases of an activating effect from adjacent heteroatoms. Davies has emphasised that accomplishing successful asymmetric C–H insertion is a delicate balancing act, hinging on the reactivity profile of the metallocarbenoid dictated from "*a judicious selection of catalyst, reagent and substrate*."[116]

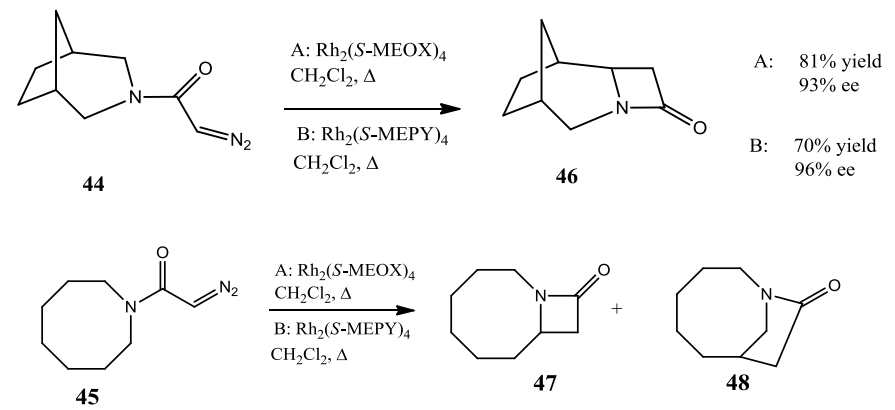
1.5.2.1.1 Intramolecular C–H insertion

Hashimoto and co-workers have carried out cyclisation of diazoamide **39** as a strategy towards formation of β-lactams through an intramolecular C–H insertion (**Scheme 1.25**).[122] Use of a chiral rhodium(II) catalyst resulted in selective formation of the β-lactam **40** in both high yield and enantioselectivity (96% ee) to provide access to the carbapenem product. A similar strategy was followed in the synthesis of a trienam intermediate, which progressed *via* enantioselective C–H insertion reaction of **41** to furnish the β-lactam **42** in good yield and high enantioselectivity (84% ee), with further functionalisation providing the desired product **43**.



Scheme 1.25

Some other interesting examples leading to β-lactam formation from azacyclic systems **44** and **45** were reported by Doyle (**Scheme 1.26**).[123] The transition metal-catalysed cyclisation of 3-diazoacetyl-3-aza-bicyclo[3.2.2]nonane **44** gave the β-lactam **46** in high yield and in high enantiopurity, whereas the diazoamide **45** afforded β- and γ-lactams **47** and **48** respectively (**Table 1.1**).

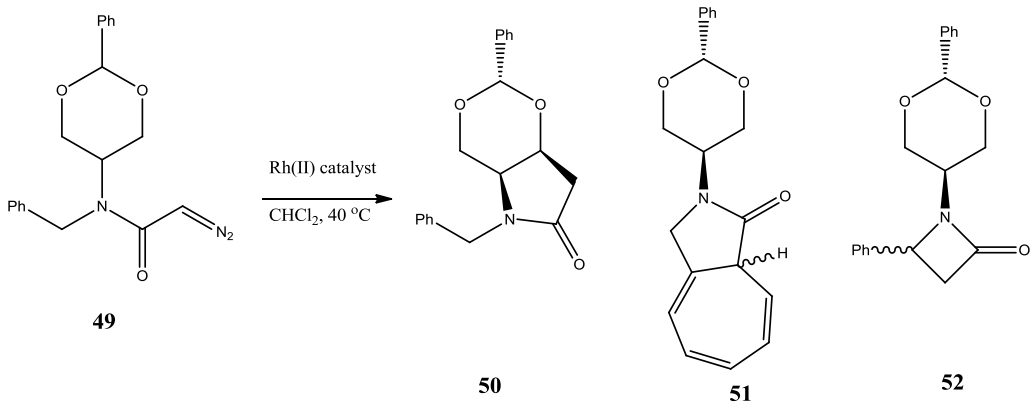


Scheme 1.26

Table 1.1

Entry	Catalyst	Yield (%)	47 : 48	ee (%) 47	ee (%) 48
1	Rh_2(*S*-MEOX)$_4$	95	26 : 74	15	98
2	Rh_2(*S*-MEPY)$_4$	97	40 : 60	31	97

It has been shown that where competing reactions are possible, formation of products can be controlled using different catalysts. An interesting example of this has been described by Doyle for the rhodium(II)-catalysed cyclisations of *trans*-5-(*N*-benzyldiazoacetamido)-2-phenyl-1,3-dioxane **49** (**Scheme 1.27**),[124,125] where competition occurs between C–H insertion of the bond adjacent to oxygen, aromatic addition and benzylic C–H insertion. A wide range of Doyle's chiral rhodium(II) catalysts have proven capable of effecting these transformations affording different ratios of the three possible products **50**, **51** and **52** (**Table 1.2**, entry 4 *vs.* 5). The most selective catalyst observed was Rh_2(*S*-MEPY)$_4$, giving rise almost exclusively to the γ-lactam **50** in 75% yield and 85% ee. A general trend observed was that the more electron-deficient catalysts, *e.g.* Rh_2(*S*-TBSP)$_4$ (**Table 1.2**, entry 5), tended to form more of the aromatic addition product, with little tendency towards formation of the γ-lactam and elimination of the β-lactam pathway.



49 **50** **51** **52**

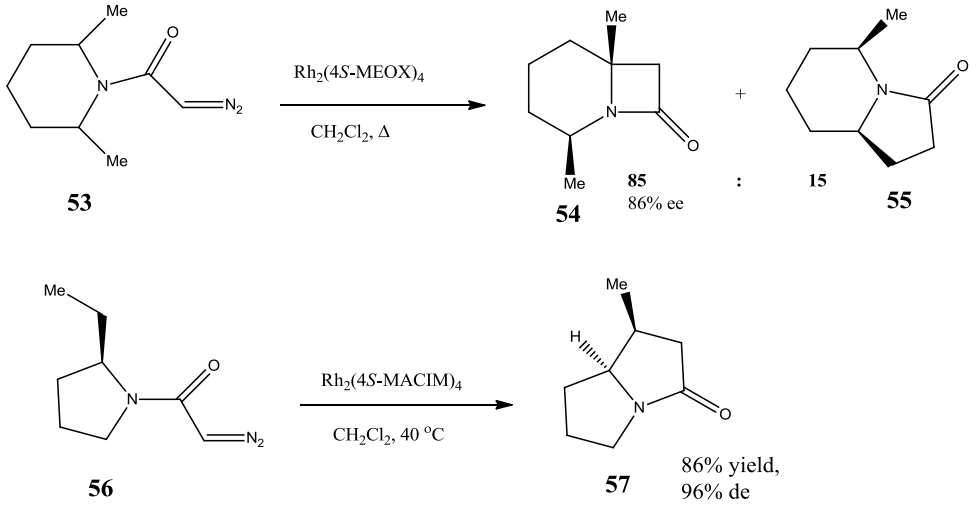
Scheme 1.27

Table 1.2

Entry	Catalyst	50 : 51 : 52	Yield 50 (%)	ee 50 (%)
1	$Rh_2(OAc)_4$	43 : 57 : 0	22	–
2	Rh_2(5*S*-MEPY)$_4$	95 : 5 : 0	75	85
3	Rh_2(4*S*-IBAZ)$_4$	49 : 35 : 16	45	19
4	Rh_2(5*S*-MPPIM)$_4$	53 : 18 : 29	48	37
5	Rh_2(*S*-TBSP)$_4$	22 : 78 : 0	9	56

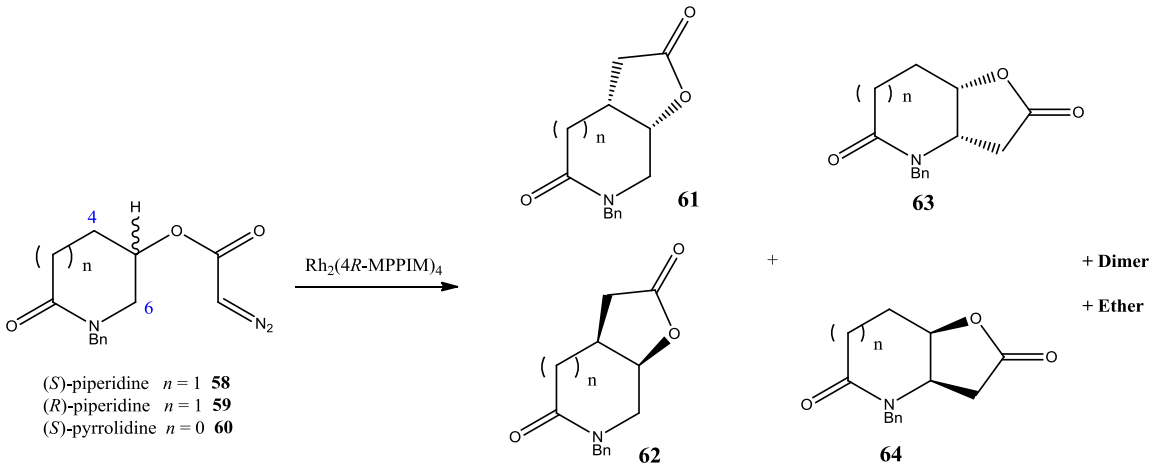
In work carried out by Doyle,[123,126] a similar method was followed using *N*-substituted piperidines and *N*-substituted pyrrolidines as substrates for intramolecular C–H insertion (**Scheme 1.28**). Competing sites for C–H insertion allow generation of either the β-lactam or the γ-lactam. In the case of the piperidine system **53**, there is a clear preference for formation of β-lactam **54** over the γ-lactam **55**. Doyle has postulated this is due to a preferential chair conformation in the transition state with the methyl groups taking up axial orientations avoiding steric interaction with the acetyl group.[123] Alternatively, this may be simply as a result of preferential insertion into a C–H bond rather than CH_2. For the pyrrolidine substrate

56, the γ-lactam product **57** was prepared exclusively in high yield and excellent diastereoselectivity (96% de).[126]



Scheme 1.28

In 2009, Wee and co-workers published results pertaining to regio- and diastereocontrol in C–H insertions of piperidine and pyrrolidine α-diazoacetates **58-60** applicable for the formation of bicyclic lactones (**Scheme 1.29**).[127] This work builds on earlier efforts by Wee involving protected pyrrolidines in the formation of (–)-turneforcidine.[128] After extensive catalyst studies, it was found that Rh_2(4*S*-MPPIM)$_4$ and Rh_2(4*R*-MPPIM)$_4$ were the optimal catalysts for C–H insertion of (*S*)-piperidine, (*R*)-piperidine and (*S*)-pyrrolidine substrates **58-60**, with the outcome strongly influenced by the stereochemistry of the catalyst. For the piperidine system **58** or **59**, there is the possibility of two sites for C–H insertion, at C(4)–H to furnish **61** or **62** and at C(6)–H to afford **63** or **64**, as well as the possibility of dimerisation and ether formation. The formation of the potential side products was found to be very competitive with C–H insertion for the pyrrolidine α-diazoketone substrate **60**, with high amounts of dimer and ether product obtained and complete absence of carbenoid insertion at C(4)–H (**Table 1.3**).

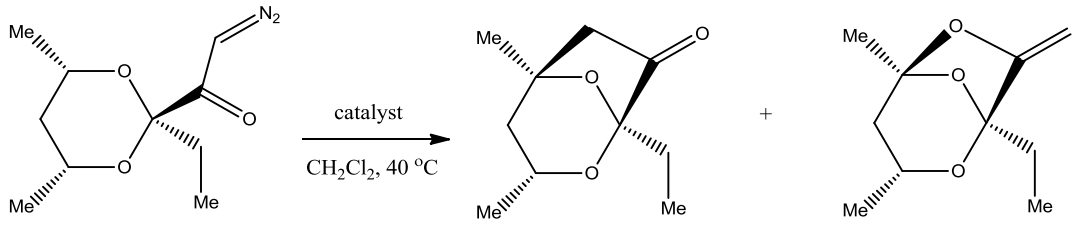


Scheme 1.29

Table 1.3

Entry	Diazo	Catalyst	Yield (%)	Relative Yield 63/64 : 61/62	Dimer (%)	Ether (%)
1	**58**	Rh_2(4*S*-MPPIM)$_4$	87	100 : 0	–	3
2	**58**	Rh_2(4*R*-MPPIM)$_4$	86	17 : 83	–	10
3	**59**	Rh_2(4*S*-MPPIM)$_4$	84	20 : 80	–	14
4	**59**	Rh_2(4*R*-MPPIM)$_4$	85	100 : 0	–	4
5	**60**	Rh_2(4*S*-MPPIM)$_4$	n/a	70 : 0	7	11
6	**60**	Rh_2(4*R*-MPPIM)$_4$	n/a	–	–	19

Wardrop and Forslund have successfully used this methology in the desymmetrisation of a dioxane-substituted α-diazoketone **65** (**Scheme 1.30**).[129] Carbenoid insertion into the tertiary C–H bond afforded intramolecular C–H insertion product **66** as the major component for all the chiral rhodium(II) catalysts investigated, though use of $Cu(acac)_2$ as catalyst favoured formation of the bicyclic enol ether **67**, arising from a possible oxygen-mediated hydride transfer. The yields from the reaction ranged from moderate to poor, while low enantiopurities were obtained for this transformation (**Table 1.4**).



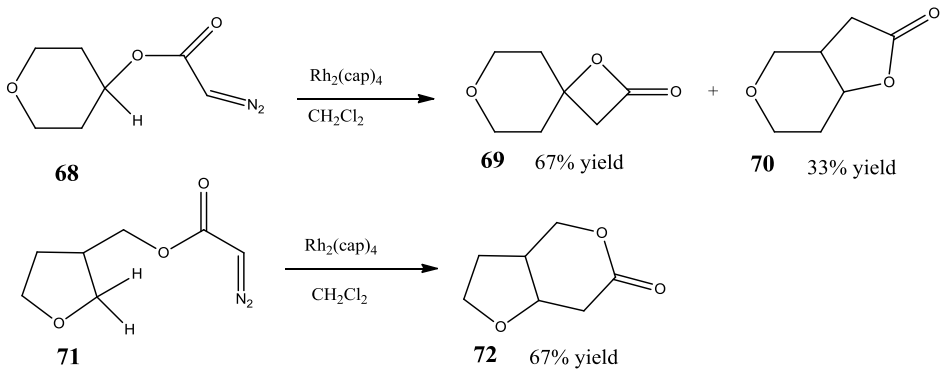
65 **66** **67**

Scheme 1.30

Table 1.4

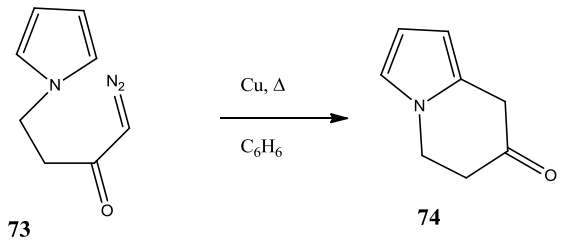
Entry	Catalyst	Ratio 66 : 67	Yield 66 (%)	ee 66 (%)
1	$Rh_2(OAc)_4$	67 : 33	58	–
2	Rh_2(*S*-PTPA)$_4$	78 : 22	36	20
3	Rh_2(*S*-DOSP)$_4$	100 : 0	31	7
4	Rh_2(*S*-TBSP)$_4$	77 : 23	17	>5
5	Rh_2(*S*-MEPY)$_4$	58 : 42	11	>5
6	$Cu(acac)_2$	33 : 67	15	–

Doyle has also synthesised lactones *via* the catalytic C–H insertion of 4-substituted pyran derivative **68** in high yields resulting in formation of both spirocyclic β-lactone **69** and the γ-lactone **70**.[130] The spirolactone **69** arises from C–H insertion into the oxygen-activated tertiary C–H bond rather than the unactivated secondary C–H bond (**Scheme 1.31**). In the case of the analogous tetrahydrofuran system **71**, C–H insertion into the C(2)–H bond activated by the ethereal oxygen proceeded almost exclusively to provide **72**, with just a trace amount of spirolactone observed.

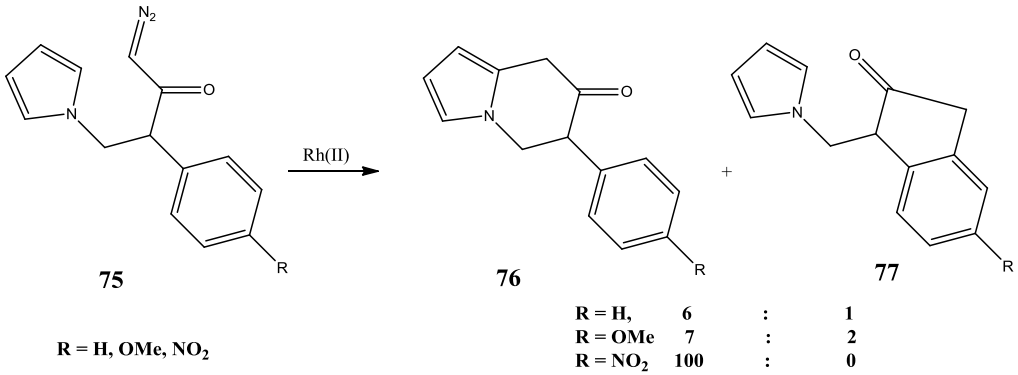


Scheme 1.31

In 1983, Muchowski[131] carried out the first intramolecular carbenoid insertions to pyrroles at the C(2)–H position using α-diazoesters and shortly thereafter Jefford reported cyclisations of pyrrole-containing α-diazoketone **73** to prepare the bicyclic indolizidine skeleton **74** in quantitative yield (**Scheme 1.32**).[132] Further investigations by Jefford and Johncock focused on *N*-substituted α-diazoketones containing an aromatic ring attached to the side-chain (**Scheme 1.33**).[133] In the transition metal-catalysed transformation of α-diazoketone **75**, competing intramolecular insertion was observed, between C–H insertion at C(2)–H of the pyrrole ring to provide **76** or into the available aromatic C–H to generate **77**. The cyclisation strongly favoured insertion into the pyrrole ring to afford the dihydroindolizinone, with high yields obtained in all cases.



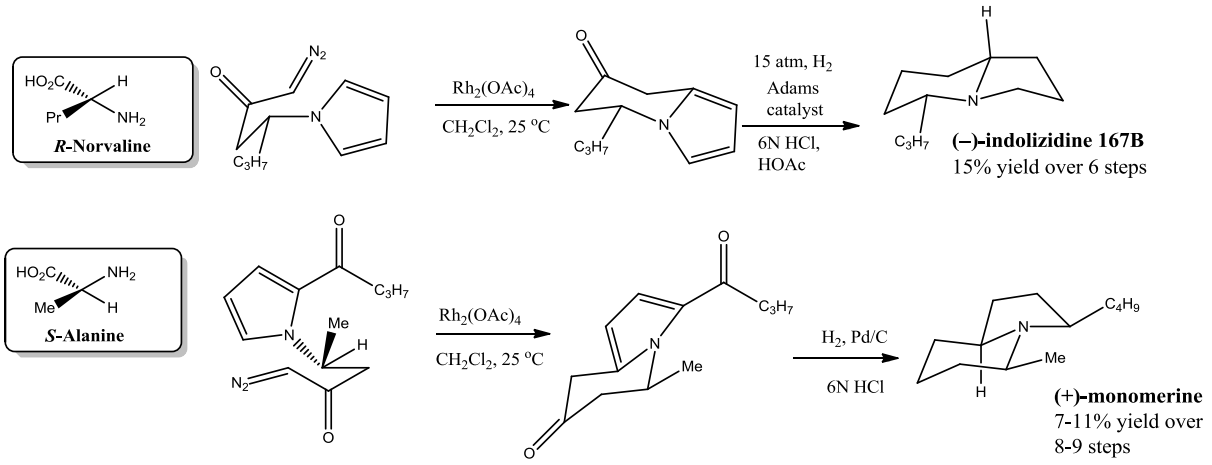
Scheme 1.32



Scheme 1.33

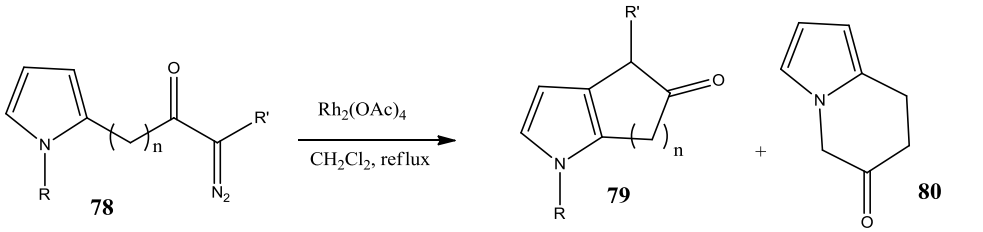
Jefford exploited this selective C–H insertion in the synthesis of alkaloids (±)-ipalbidine, (–)-indolizidine 167B and (+)-monomerine (**Scheme 1.34**), where the pyrrole compounds were derived from naturally occurring α-amino acids and β-amino acids from the chiral pool.[134,135] In each case, the cyclisation is a key stage in the synthesis followed by hydrogenation to the

alkaloids in an overall 6–9-step sequence depending on the substrate. The chirality induced from early-stage introduction of the amino acids is fully retained in the products, providing an efficient route for the enantioselective synthesis of alkaloid targets.



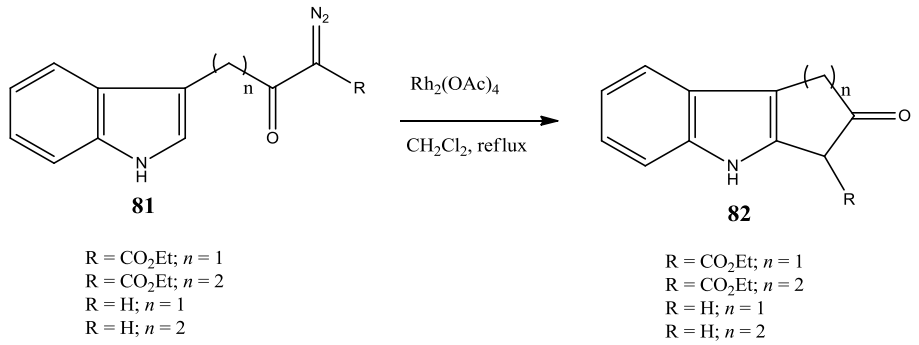
Scheme 1.34

Cuevas-Yañez *et al.* have examined cyclisation pathways of 2-substituted pyrrole α-diazoketones or esters (**Scheme 1.35**) as well as 3-substituted indole α-diazoketones and esters (**Scheme 1.36**).[136] In the cyclisations of 2-substituted pyrrole derivatives **78** the expected C–H insertion products **79** were generated. A competitive N–H insertion pathway to afford **80**, in addition to formation of C–H insertion product **79** was observed when the pyrrole nitrogen was unsubstituted (R = H, *n* = 2, R' = H), although the reaction outcome still favoured generation of **79**. However, alkylation of the N–H bond precluded the N–H insertion reaction.



Scheme 1.35

Carbenoid-mediated reactions of indole α-diazocarbonyl compounds **81** furnished the expected tricyclic products **82** in moderate yields *via* intramolecular C–H insertion into C(2)–H of the indole ring (**Scheme 1.36**). In addition, Durst had previously reported insertion into aromatic C–H bonds of thienyl- and *N*-SO_2Ph indole-containing α-diazo-β-sulfonyl esters resulting in the generation of sulfolanes.[137] There would appear to be some similarities between the chemistry discussed here and in the later section concerning intramolecular cyclopropanation (**Section 1.5.4.2**). The discrepancy is that in the above work, the authors have identified a C–H insertion pathway,[133,135,136] whereas Padwa and Capretta have credited the reaction pathway to cyclopropanation followed by ring scission.[138-142]



81

R = CO_2Et; *n* = 1
R = CO_2Et; *n* = 2
R = H; *n* = 1
R = H; *n* = 2

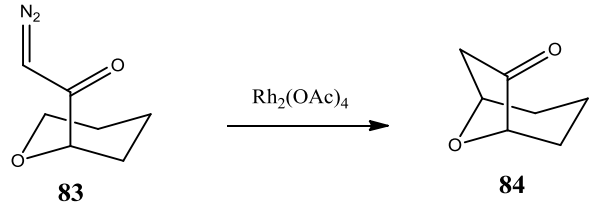
82

R = CO_2Et; *n* = 1
R = CO_2Et; *n* = 2
R = H; *n* = 1
R = H; *n* = 2

Scheme 1.36

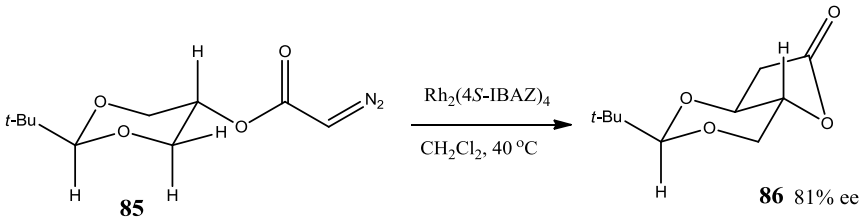
Studies by Adams illustrated the activation of an α-methylene group by the presence of an ethereal oxygen for substrate **83**, favouring C–H insertion at C(6)–H to furnish the bridged cyclic ether **84** (**Scheme 1.37**).[143]

Doyle has investigated similar systems containing two ether oxygens as well as phenyl and *tert*-butyl substituents in the γ-position to the side-chain containing the diazo functionality (**Scheme 1.38**).[144] Reaction of the *tert*-butyl substituted α-diazocarbonyl substrate **85** gave the acetal **86** as product in high enantioselectivity (81% ee). Replacement of *tert*-butyl group with a phenyl group for **87** gave a different acetal product **88**, arising from insertion into the axial C–H bond at C(2)–H. The bicyclic lactone **88** showed a high degree of asymmetric induction (**Table 1.5**), with the Rh_2(5*R*-MEPY)$_4$ catalyst proving particularly effective (94% ee) (**Table 1.5**, entry 4). Doyle has ascribed formation of **88** to axial C–H bond specific electronic stabilisation of the transition state by the phenyl group.

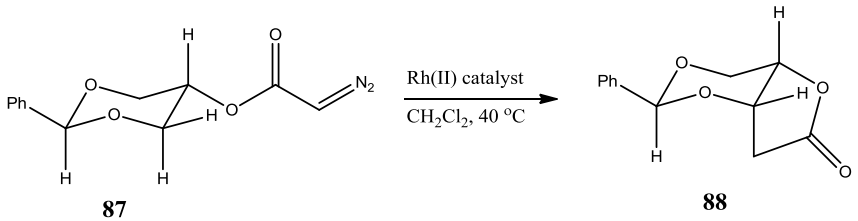


83 **84**

Scheme 1.37



85 **86** 81% ee



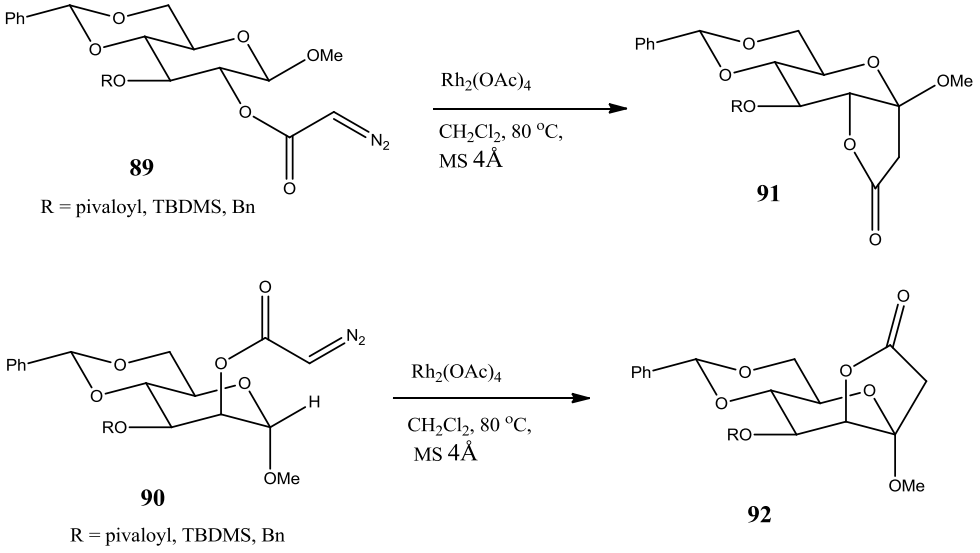
87 **88**

Scheme 1.38

Table 1.5

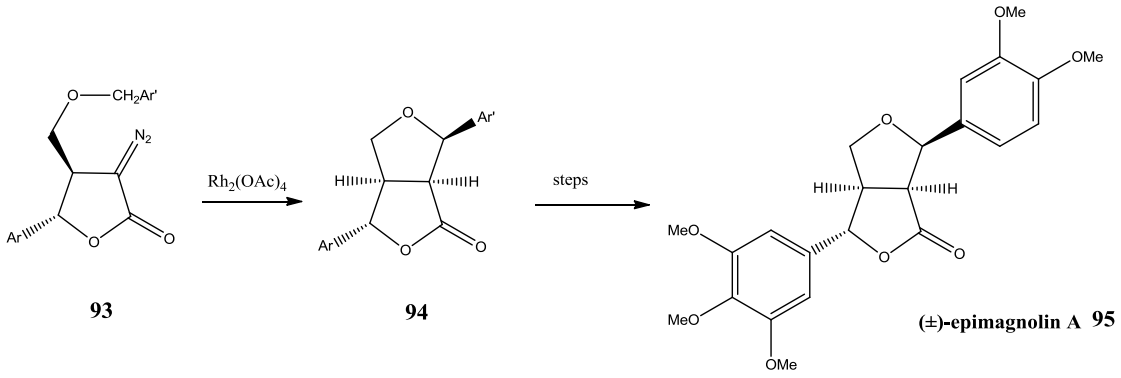
Entry	Catalyst	Yield 88 (%)	ee (%)
1	Rh_2(4*S*-IBAZ)$_4$	85	88
2	Rh_2(4*S*-MEOX)$_4$	48	67
3	Rh_2(5*S*-MEPY)$_4$	71	94
4	Rh_2(5*R*-MEPY)$_4$	75	94

An intramolecular C–H insertion of more complex carbohydrate-based α-diazoester has been demonstrated by Lecourt and co-workers (**Scheme 1.39**).[145] The different anomeric precursors **89** and **90** furnished the α- and β-ketopyranosides **91** and **92** with the pivaloyl and *tert*-butyldimethylsilyl (TBDMS) protecting groups found to provide better outcomes than the benzyl protecting group. In the case of the benzyl-protected α-diazoketone, a competing 1,7-insertion into the benzylic position was observed in significant amounts.



Scheme 1.39

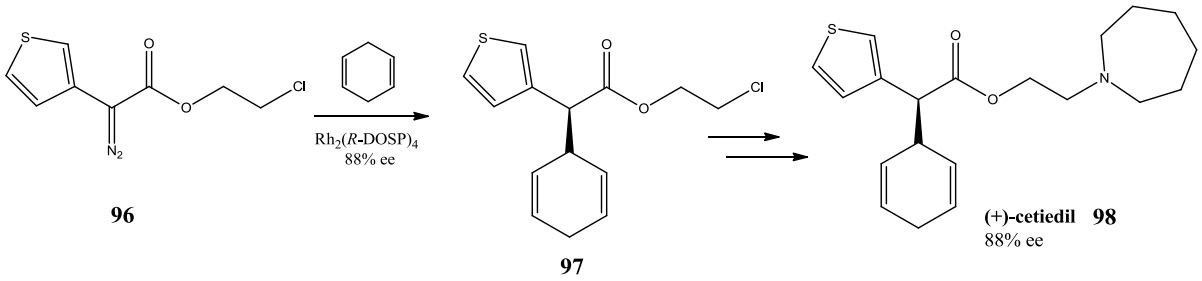
Brown and Hinks have synthesised *endo*, *exo*-furofuranones utilising an intramolecular C–H insertion approach (**Scheme 1.40**).[146] Stereoselective ring closure to the activated benzylic group of the α-diazo-γ-butyrolactone **93** enabled generation of the bicyclic framework of **94**, with installation of the desired stereochemistry. This strategy has led to the synthesis of the furofuran lignan, asarinin, and (±)-epimagnolin A **95**.[147]



Scheme 1.40

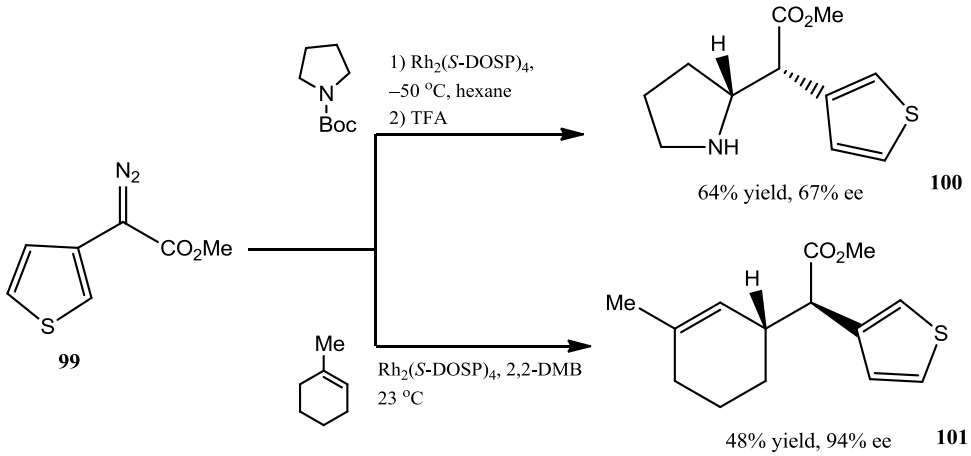
1.5.2.1.2 Intermolecular C–H insertion

While the literature is replete with examples of intramolecular C–H insertion, there are also several useful examples involving intermolecular C–H insertion reactions of heterocyclic α-diazocarbonyl compounds. Davies has employed this methodology in the synthesis of (+)-cetiedil **98** (**Scheme 1.41**).[148] The donor/acceptor α-diazoester **96** is a precursor to a donor/acceptor metallocarbenoid system, which are very suitable substrates for highly enantioselective intermolecular C–H insertion (**Section 1.5.4.1**). Similar donor/acceptor substrates have been explored by Davies regarding asymmetric intermolecular cyclopropanation of heteroaryldiazoacetates.[45] After screening a range of dienes in the intermolecular C–H insertion, 1,4-cyclohexadiene gave the optimal results with less of the competing cyclopropanation product observed than with other dienes. The thiophenyldiazoacetate **96** provided the C–H insertion product **97** in moderate yield and high enantioselectivity (88% ee). The insertion product **97** was subsequently converted to cholinsterease inhibitor (+)-cetiedil **98** in high yield after two further steps with excellent stereoretention observed (88% ee).



Scheme 1.41

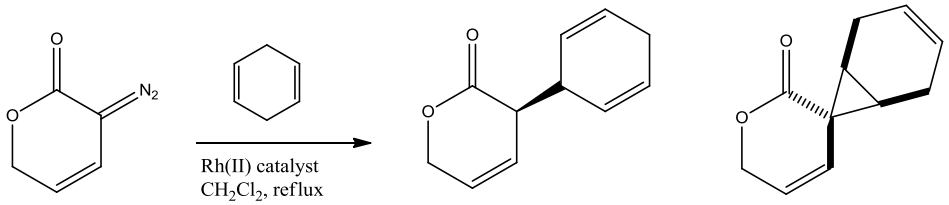
Davies and co-workers have reported intermolecular C–H insertions utilising the related methyl 2-diazo-2-(thiophen-3-yl)acetate **99**, with effective C–H activation into *N*-Boc-pyrrolidine and 1-methyl-1-cyclohexene (**Scheme 1.42**).[148] The C–H insertion products **100** and **101** were synthesised in modest to good yield, though moderate to excellent enantiopurities of 67% ee and 94% ee were achieved.



Scheme 1.42

In 2006, further intermolecular C–H insertion was disclosed by Doyle where vinyldiazolactone **102** underwent C–H insertion with 1,4-cyclohexadiene (**Scheme 1.43**).[149] In all instances, cyclopropanation was observed as a competing reaction outcome to the C–H insertion pathway, though this pathway can be successfully suppressed by careful choice of the catalyst system (**Table 1.6**). The chiral rhodium(II) carboxamidate catalysts strongly

favoured formation of C–H insertion product **103**, though in the case of the enantiopure rhodium(II) carboxylate catalyst, Rh_2(*S*-DOSP)$_4$ (**Table 1.6,** entry 2), formation of cyclopropane **104** was the dominant reaction with almost complete elimination of the C–H insertion pathway. The Rh_2(MenthAZ)$_4$ catalysts (**Table 1.6**, entries 5 and 6) were found to superior for chemoselectivity and enantioinduction.



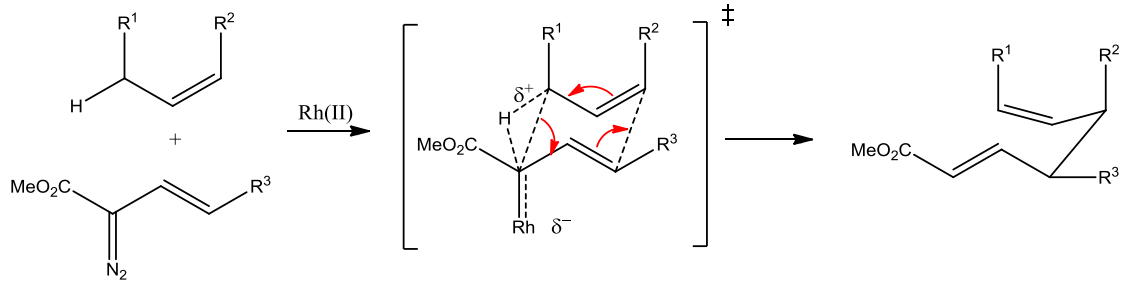
102 **103** **104**

Scheme 1.43

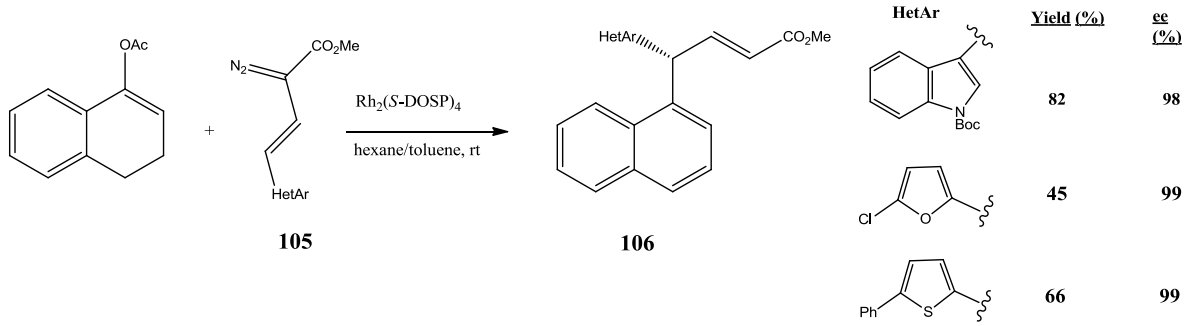
Table 1.6

Entry	Catalyst	103 : 104	Yield 103 (%)	ee 103 (%)
1	$Rh_2(OAc)_4$	2 : 3	53	–
2	Rh_2(*S*-DOSP)$_4$	1 : 9	56	18
3	Rh_2(*S*-MEPY)$_4$	4 : 1	47	8
4	Rh_2(*S*-MEAZ)$_4$	9 : 1	43	60
5	Rh_2(*S*,*S*-MenthAZ)$_4$	9 : 1	42	79
6	Rh_2(*S*,*R*-MenthAZ)$_4$	9 : 1	50	80

Davies has examined an interesting transformation of vinyl carbenoids by using a combined intermolecular C–H activation/Cope rearrangement strategy,[150] later termed the CHCR strategy.[151] The C–H insertion product was found to be the most thermodynamically stable product, arising from C–H functionalisation with synchronous Cope rearrangement, as illustrated below (**Scheme 1.44**). Numerous heteroarylvinyl α-diazoacetates **105** were used in this study with varying degrees of success (**Scheme 1.45**).[150] Reaction of **105** with Rh_2(*S*-DOSP)$_4$ resulted in enantiopreferential formation of rearrangement products **106** in moderate to high yield.



Scheme 1.44: General example of Cope rearrangemement and illustration of 'chair-like' transition state[150,151]



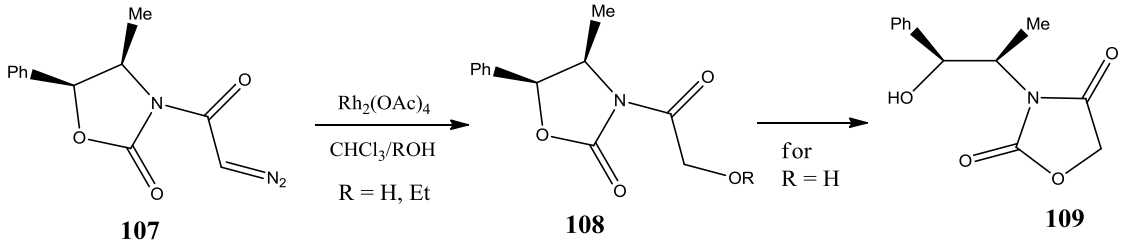
105 106

Scheme 1.45

1.5.2.2 O–H insertion and 'O'–insertion

The O–H insertion pathway can be induced by thermal, photochemical, and acid- or transition metal-catalysed reactions, generating a new ethereal C–O linkage in the process. Insertion reactions by carbenes and/or carbenoids into O–H bonds generally employ water, alcohols, phenols, carboxylic acids and sulfonic acids as the O–H source. Among the earliest attempts to explore the metallocarbenoid reactions were investigations by Teyssié *et al*. using rhodium(II) acetate with water and alcohols.[152,153] In addition, a comprehensive review of the scope of this methodology has been published by Moody and Miller in 1995.[154]

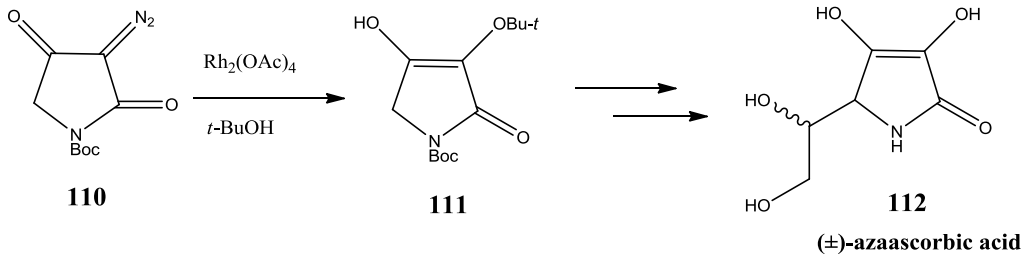
Doyle investigated the O–H insertion reactions of chiral oxazolidinones in water/chloroform (**Scheme 1.46**).[155] Insertion of the water/chloroform into the rhodium carbenoid derived from **107** afforded O–H insertion product **108** in excellent yield. The oxazolidinedione **109** is thought to arise *via* internal *trans* esterification of the hydroxy intermediate **108**.



107 108 109

Scheme 1.46

The intermolecular O–H insertion strategy can be applied towards the synthesis of (±)-azaascorbic acid **112** by reaction of **110** with rhodium(II) acetate and *tert*-butyl alcohol (**Scheme 1.47**).[156] After a series of functional group interconversions from O–H insertion product **111**, the desired aza-analogue of ascorbic acid **112** was successfully prepared. In general, O–H insertions into rhodium carbenoids occurs under very mild conditions when compared to Lewis or Brønsted acid catalysis, making it a more desirable method for O–H insertion.

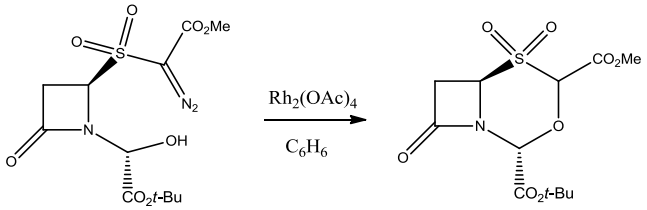


110 111 112

(±)-azaascorbic acid

Scheme 1.47

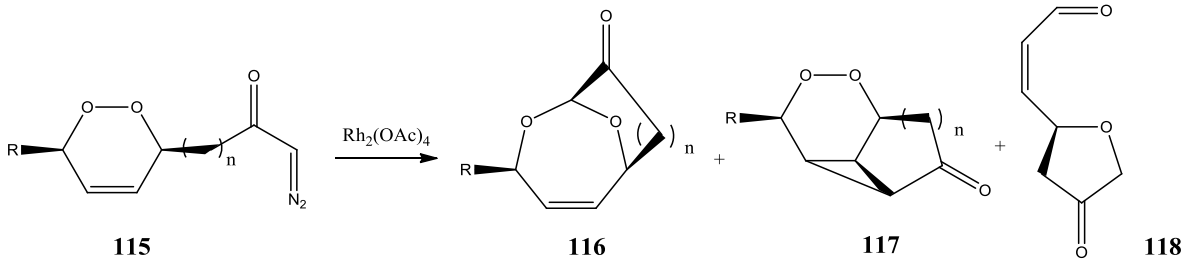
Employment of an intramolecular O–H insertion reaction can lead to generation of medium-sized ring ethers (4–8-membered rings). Crackett has reported efficient O–H insertion of a suitably substituted β-lactam derivative **113**, leading to the formation of the bicyclic oxacepham product **114** in 58% yield (**Scheme 1.48**).[157]



113 **114** 58% yield

Scheme 1.48

In more recent times, Taylor has demonstrated examples of carbenoid insertion into a peroxide linkage, in competition with an intramolecular cyclopropanation reaction for 3,6-dihydro-1,2-dioxines **115**, leading to formation of bicyclic acetals and tricyclic peroxides (**Scheme 1.49**).[158] Three products were isolated from the reaction mixture; the peroxide-bond insertion **116** was observed as the major component, with tricyclic peroxide **117** and aldehyde **118** also isolated (**Table 1.7**). However, the higher homogues (*n* = 2, **Table 1.7**, entries 4 and 5) did not generate any of **116** or **117**. An interesting note from earlier work by Avery and Taylor is the corresponding intermolecular carbene insertion (generated from stabilised phosphorous ylides) on the parent 1,2-dioxine did not proceed into either the peroxide linkage or the olefin.[159]



115 **116** **117** **118**

R = H, Me, Ph
n = 1, 2

only for R = H, *n* = 1

Scheme 1.49

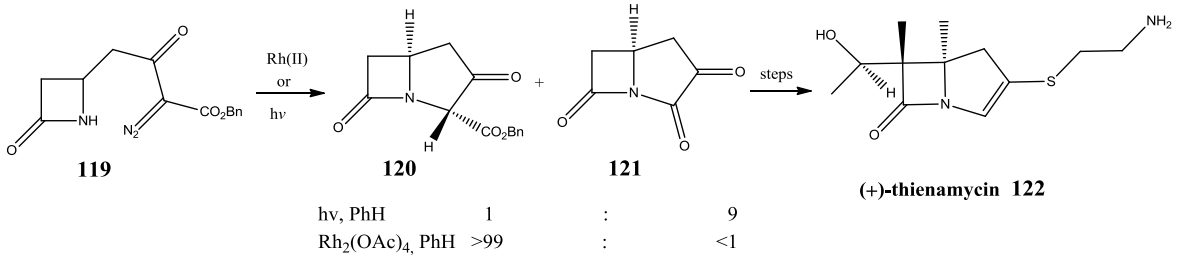
Table 1.7

Entry	R	*n*	Yield 116 (%)	Yield 117 (%)	Yield 118 (%)
1	Me	1	41	14	0
2	Ph	1	62	11	0
3	H	1	32	0	8
4	H	2	–	–	–
5	Ph	2	–	–	–

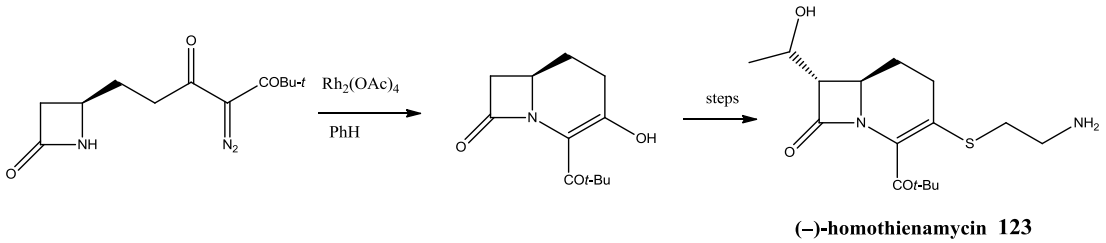
1.5.2.3 N–H insertion

1.5.2.3.1 Intramolecular N–H insertion

In 1978, researchers at Merck reported intramolecular insertion of a metal-stabilised carbene into the N–H bond of a β-lactam, providing access to the carbapenem nucleus.[160] Subsequent work by Christensen in 1980 applied this strategy to the industrial synthesis of the antibiotic (+)-thienamycin **122** (**Scheme 1.50**).[161] Conversion of **119** to β-lactam **120** proceeded with near exclusivity employing rhodium(II) acetate as catalyst, comparing very favourably to the 1 : 9 ratio of β-lactam **120** to imide byproduct **121** from the corresponding photolysis reaction. The β-lactam **120** allowed easy access to (+)-thienamycin **122** after a short synthetic sequence. Extension of this intramolecular N–H insertion methodology was applied to the production-scale synthesis of the higher homologue, (–)-homothienamycin **123** (**Scheme 1.51**).[162]



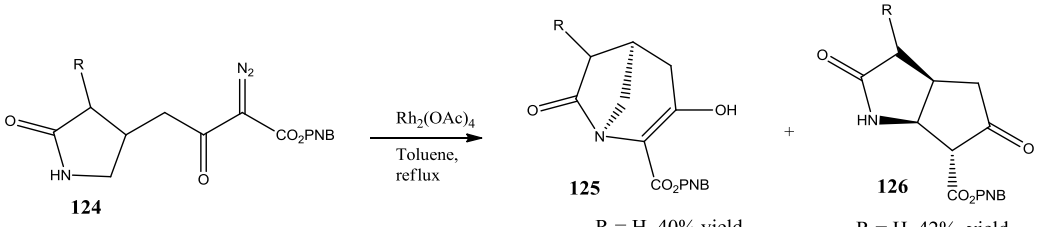
Scheme 1.50



Scheme 1.51

The β-lactam framework represents a cornerstone for targeted-design of antibiotics and this highly efficient synthesis of strained fused β-lactams was a seminal moment for N–H carbenoid insertions. Several examples of strained bicyclic β-lactams have been described (carbapenam,[163] oxapenam,[164] carbacepham,[165] oxacepham[166]), all of which have been prepared from functionalised azetidine-derived α-diazocarbonyl substrates.

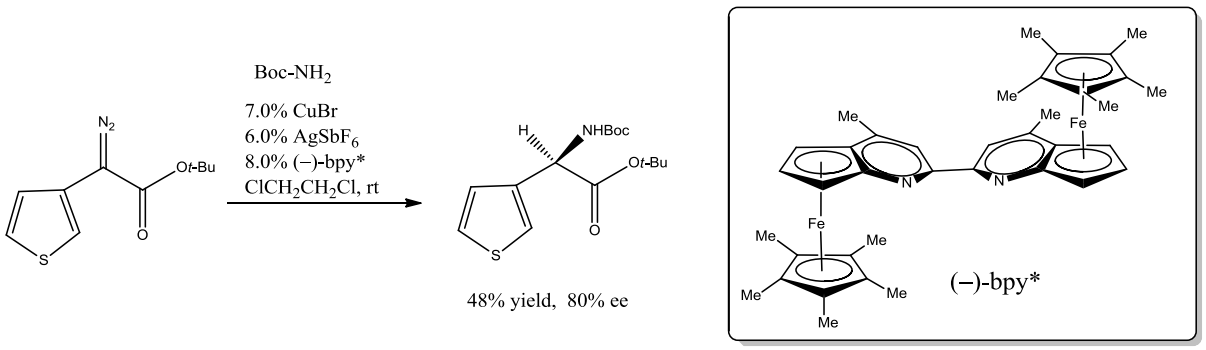
Further intramolecular insertion of carbenoids into N–H bonds of γ-lactams has been demonstrated by Lampilas resulting in the assembly of bridged lactams (**Scheme 1.52**).[167] In this process, treatment of **124** with rhodium(II) acetate yielded the bridged γ-lactam **125** and the corresponding C–H insertion product **126** in roughly equal yields. However, introduction of an ethyl group to the cyclic amine dramatically favoured the formation of the C–H insertion product **126**.



Scheme 1.52

1.5.2.3.2 Intermolecular N-H insertion

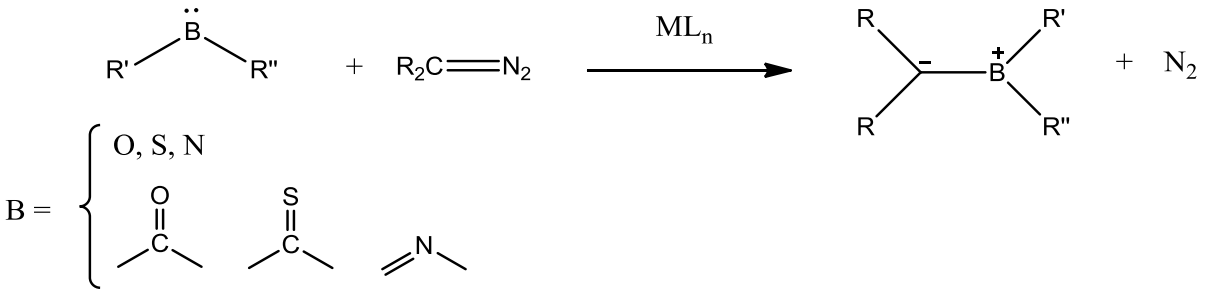
In 2007, Fu and Lee reported significant progress in enantioselective N–H insertion of carbenes using copper/planar chiral ferrocene bipyridine catalysts (**Scheme 1.53**).[168] The α-diazoesters were coupled with carbamates to furnish a range of Cbz- and Boc-protected arylglycines which can undergo facile deprotection to afford enantiopure α-amino acids. Substrate scope included substituted phenyl derivatives while the thiophene system was also utilised in this reaction, with 80–98% asymmetric induction achieved in all cases, thereby offering a general method towards enantioselective N–H insertion of α-diazocarbonyl substrates.



Scheme 1.53

1.5.3. Ylide Formation

An available Lewis Base (B:) can be readily intercepted by carbenes or metallocarbenoids to provide ylides. These compounds can be formally defined as a positively charged heteroatom connected to an adjacent carbon atom possessing an unshared pair of electrons as shown below (**Scheme 1.54**). The highly reactive intermediates from ylide-based chemistry provide a rich seam of synthetic and mechanistic discussion which has been highlighted in several extensive reviews.[6,169,170] Transformations of ylides can proceed intermolecularly or intramolecularly under mild conditions with common reaction pathways including [2,3]-sigmatropic rearrangement of allyl and propargyl substituted ylides; [1,2]-insertion or Stevens rearrangement; β-hydride elimination; and 1,3-dipolar cycloaddition of carbonyl, thiocarbonyl and azomethine ylides.

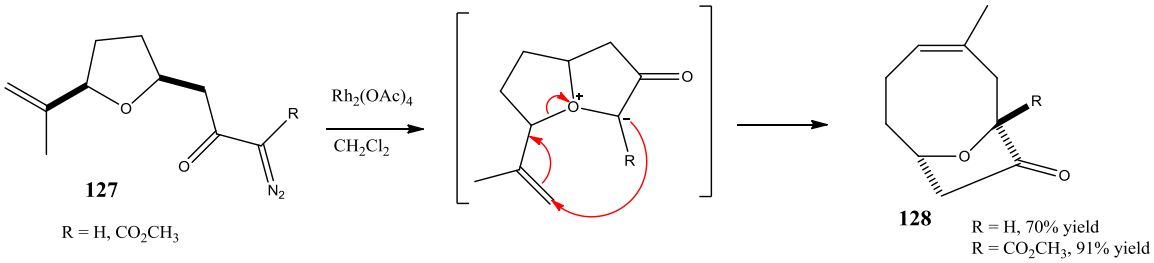


Scheme 1.54

1.5.3.1 Oxonium ylides

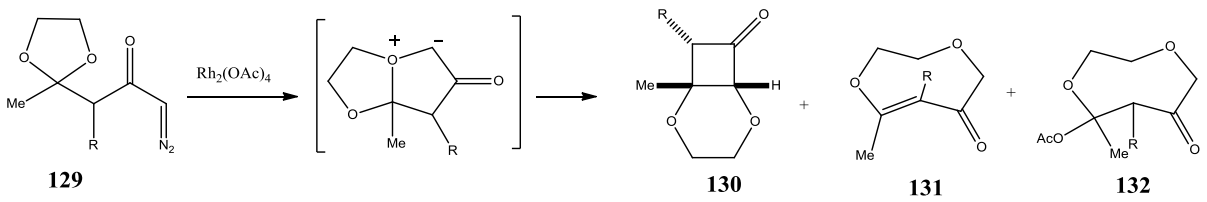
Stable oxonium ylides have not yet been isolated although they have been postulated as highly reactive intermediates. However, spectroscopic evidence[171] and preparation of analogous rearrangement products from more stable nitrogen and sulfur containing ylides has provided tangible evidence for their existence.[172] These fleeting ylides rapidly undergo two primary reaction pathways, either [2,3]-sigmatropic rearrangement of allylic and propargylic ethers or [1,2]-insertion/Stevens rearrangement, while other minor reaction pathways such as [1,4]-sigmatropic rearrangements are also observed.[173] The earliest reports for generation of putative oxonium ylides was published by Nozaki and co-workers in the late 1960s.[174,175] However, in the mid-1980s, the groups of Pirrung and Roskamp independently disclosed the first examples of intramolecular oxonium ylide formation/rearrangement of α-diazocarbonyl compounds possessing cyclic ethers *via* rhodium carbenoids.

Pirrung and Werner described the sequential ylide formation/rearrangement of a tetrahydrofuran substituted α-diazocarbonyl compound **127** possessing a pendant vinylic group. Intramolecular formation of allylic oxonium ylides/[2,3]-sigmatropic rearrangement provided the ring-expanded oxygenated heterocycle **128** (**Scheme 1.55**).[176] In the same work, Pirrung utilised acyclic allyl substituted ethers to synthesise of five- and six-membered heterocycles *via* tandem oxonium ylide generation and [2,3]-rearrangement.[176]



Scheme 1.55

Roskamp and Johnson concurrently reported intramolecular oxonium ylide formation *via* reaction of metallocarbenoid derived from acetal **129** (**Scheme 1.56**).[177] Following initial oxonium ylide construction, a Stevens rearrangement takes place; this rearrangement is particularly efficient where the migratory group is benzyl. A mixture of [1,2]-shift product **130** and elimination product **131** was observed with the former favoured (**Table 1.8**, entries 1 and 2). Later studies by Oku showed that the same transformation in the presence of acetic acid and dichloromethane formed an acetal product **132**, in addition to the elimination product **131** (**Table 1.8**, entry 3), with the saturated acetal **132** reported to originate from reaction of the enol ether with acetic acid.[178]

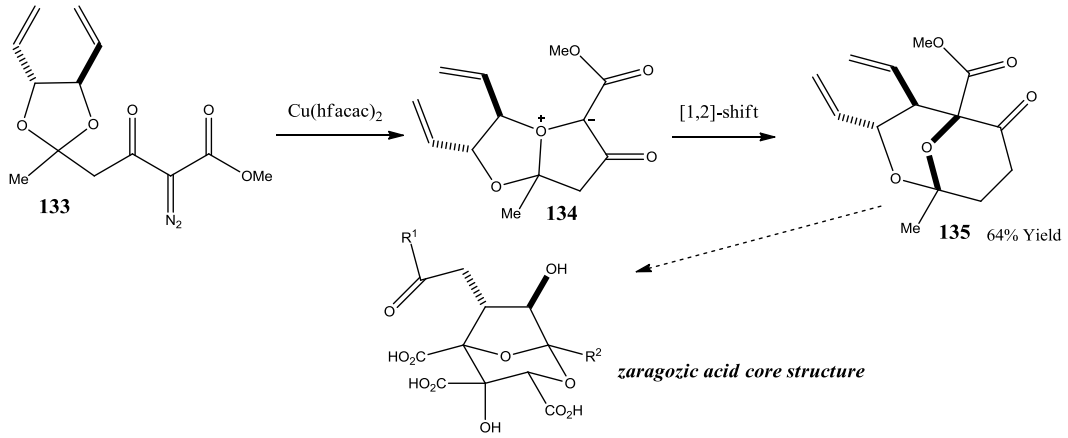


Scheme 1.56

Table 1.8

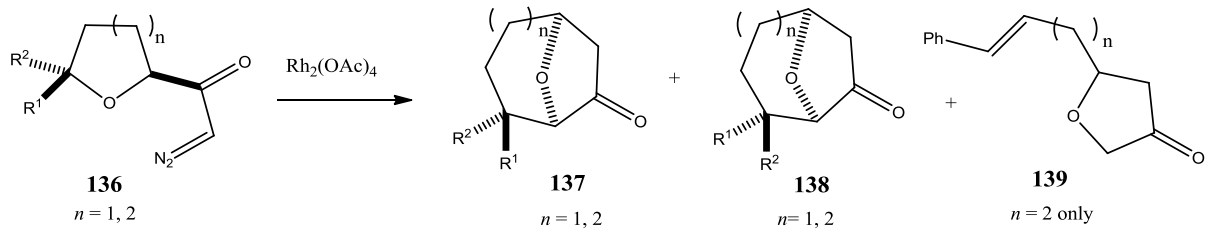
Entry	R	Conditions	Yield 130 (%)	Yield 131 (%)	Yield 132 (%)
1	H	C_6H_6, rt	68	16	–
2	Me	C_6H_6, rt	54 (97 : 3)	–	–
3	H	CH_2Cl_2, rt	0	46	41

In an extension of Roskamp's efforts on the chemistry of oxonium ylides derived from acetals, Zercher and co-workers investigated analogous α-diazo-β-ketoesters to prepare the dioxabicyclic core of the zaragozic acids (**Scheme 1.57**).[179] Treatment of α-diazo-β-ketoester **133** with $Cu(hfacac)_2$ provided the bicyclic ylide **134** arising from interaction of the metallocarbenoid with the less sterically hindered oxygen. The oxonium ylide underwent a [1,2]-shift to provide the bridged ring-expanded compound **135** and this directing effect is postulated to involve allylic stabilisation. This methodology was used to assemble a highly functionalised 2,8-dioxabicyclo[3.2.1]octane skeleton which through further synthetic embellishment can potentially provide access to the zaragozic family of natural products.[180]



Scheme 1.57

West has also utilised the formation of oxonium ylides from five- and six-membered cyclic ethers followed by [1,2]-rearrangement (**Scheme 1.58**).[181] Transition metal-catalysed cyclisation of α-diazoketones **136** afforded the bridged bicyclic ethers **137** and **138**, while an elimination product **139** was also detected for the higher homologue (n = 2) (**Table 1.9**). Cyclisation with the tetrahydrofuran substrate (n = 1) gave the bicyclic ether with predominant retention of configuration at the migrating centre, whereas cyclisation of the tetrahydropyran proceeded with complete retention of configuration.

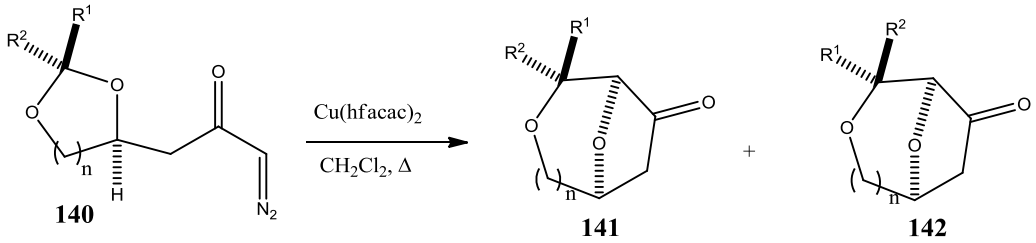


Scheme 1.58

Table 1.9

Entry	R^1	R^2	*n*	Yield 137 (%)	Yield 138 (%)	Yield 139 (%)
1	Ph	H	1	60 (**137**+**138**) (15–19 : 1)		–
2	Ph	H	2	12	0	27
3	H	Ph	1	90 (**137**+**138**) (2 : 1)		–
4	H	Ph	2	51	0	0

West further investigated the scope of acetal α-diazocarbonyl derivatives with an α-diazocarbonyl side-chain adjacent to the oxygen, but not flanked by the two oxygen atoms of the acetal (**Scheme 1.59**),[182] as seen previously.[177,179] Cyclisation of α-diazoketones **140** afforded the dioxabicyclic products **141** and **142** in high yields and use of copper(II) bis(hexafluoroacetylacetonate) as catalyst provided cleaner products than reactions involving rhodium(II) acetate (**Table 1.10**). Interestingly, reactions of analogous unsubstituted derivatives (R^1, R^2 = H) failed to generate ring-expanded products **141** and **142**.



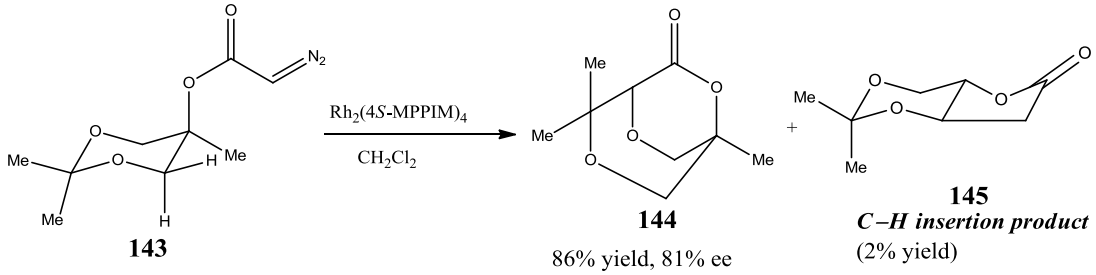
140 **141** **142**

Scheme 1.59

Table 1.10

Entry	R^1	R^2	*n*	Yield 141 +142 (%)	141 : 142
1	Ph	H	1	94	14 : 1
2	H	Ph	1	90	1 : 1.2
3	Ph,	H	2	96	1.5 : 1

Employment of chiral rhodium(II) carboxamidate catalysts by Doyle resulted in highly enantioselective oxonium ylide formation and subsequent Stevens rearrangement for 1,3-dioxan-5-yl α-diazoacetates (**Scheme 1.60**).[183] In most cases with analogous acetals, Stevens rearrangement was in competition with a C–H insertion pathway. However, cyclisation of **143** resulted in virtually exclusive formation of **144** *via* tandem catalytic oxonium ylide generation/rearrangement, as well as a minor amount of C–H insertion product **145** (2%). In instances where restricted conformation prevents the α-diazoester group being positioned in an axial position on the acetal, C–H insertion emerges as the dominant process with a diminished level of asymmetric induction observed.



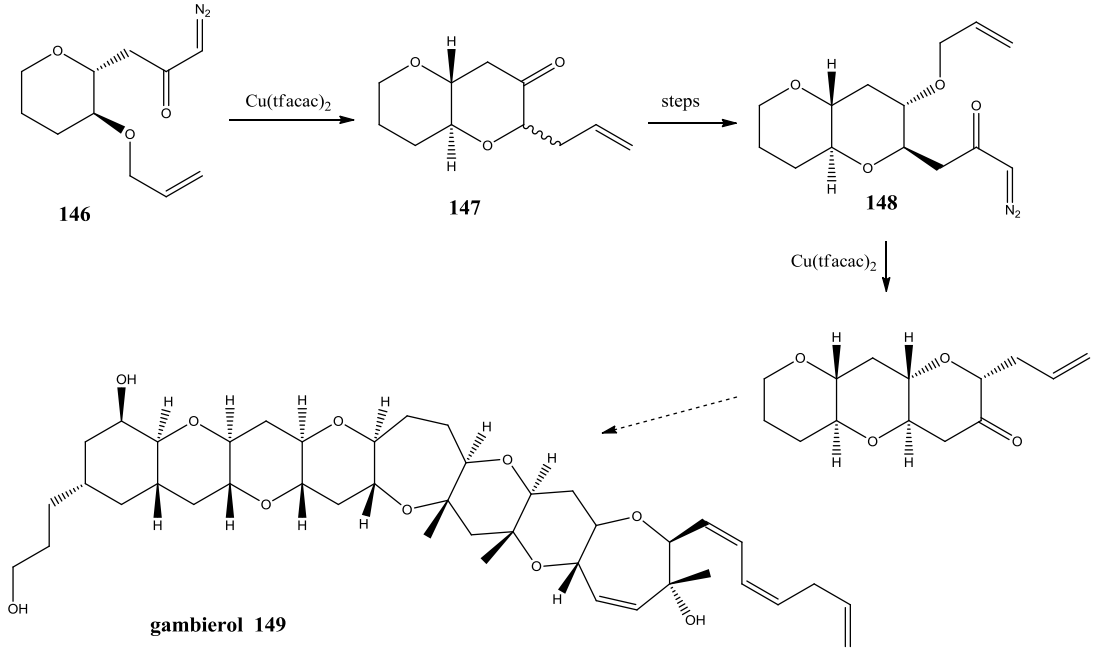
143

144
86% yield, 81% ee

145
C–H insertion product
(2% yield)

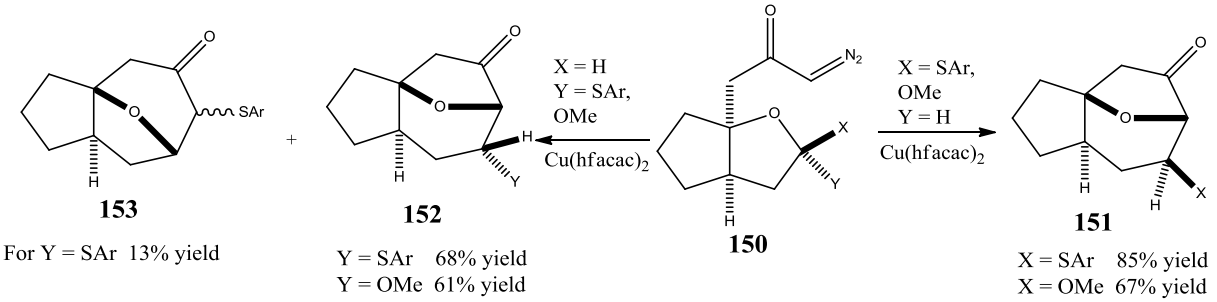
Scheme 1.60

In 2001, West and Marmsäter used the tandem ylide formation/[2,3]-sigmatropic rearrangement (**Scheme 1.61**),[184] resulting in the development of a novel iterative strategy for the synthesis of poly(tetrahydropyran)ethers employing sequential rearrangement of tetrahydropyran derived oxonium ylides. This strategy can serve as a useful approach to the synthesis of the core framework of polypyran natural products such as the marine ladder toxin, gambierol **149**. Copper-catalysed reaction of tetrahydropyran **146** led to an ylide intermediate, which underwent a [2,3]-rearrangement affording the bicylic ether **147**. Functional group manipulation of the α-substituted ketone and allyl ether groups allowed generation of α-diazoketone **148** containing contiguous allyl and diazo groups, which could be extended towards the assembly of gambierol **149**.



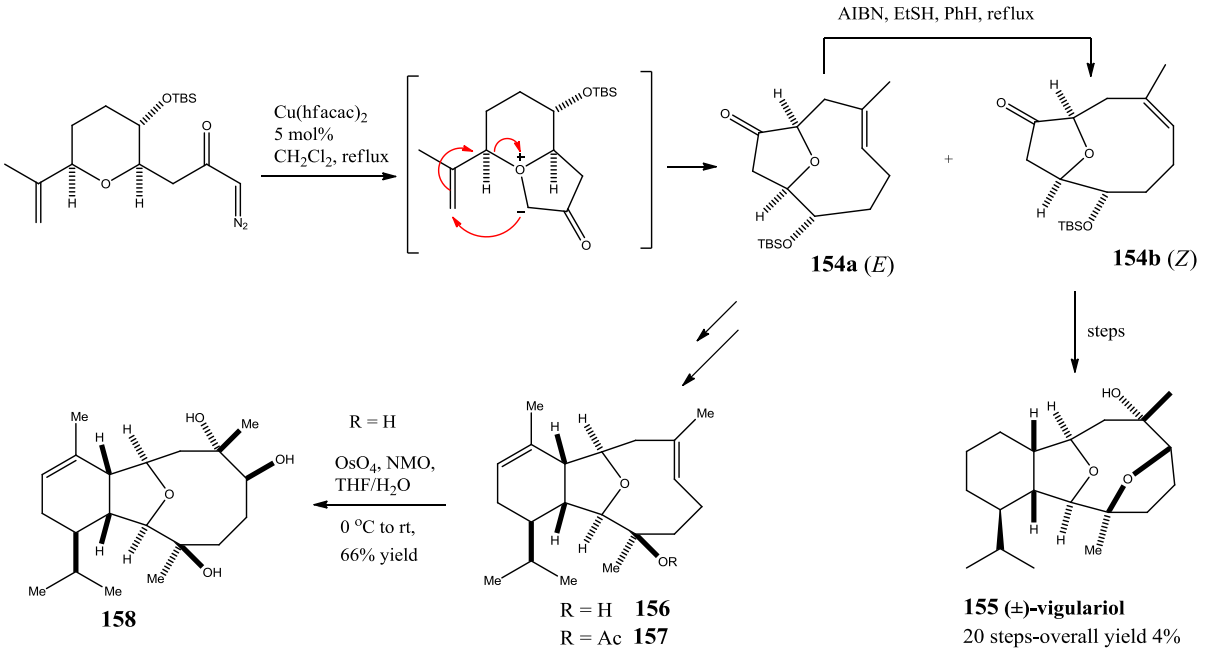
Scheme 1.61

Bicyclic mixed acetal precursors were first surveyed by Marmsäter and West in 2003 using 6,5-bicyclic α-diazocarbonyl substrates,[185] followed thereafter by Murphy and West employing 5,5-bicyclic mixed acetal α-diazoketones of type **150**. Reaction of α-diazoketone **150** in the presence of $Cu(hfacac)_2$ proceeded to give bridged hydroazulenes **151** and **152** in high yield after initial oxonium ylide formation and subsequent [1,2]-rearrangement of the anomeric carbon (**Scheme 1.62**).[186] An alternative cyclisation pathway is postulated to give rise to a minor product **153** *via* formation of a seven-membered sulfonium ylide followed by [1,2]-shift to generate the side product.



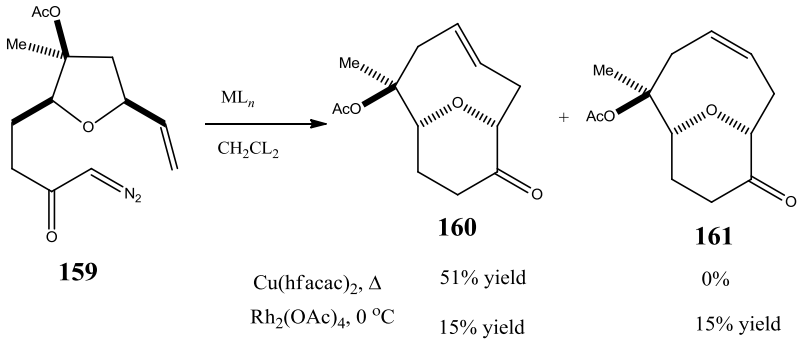
Scheme 1.62

Clark *et al*. have completed the total synthesis of (±)-vigulariol **155**, a bridged tricyclic marine natural product (**Scheme 1.63**).[187] The pivotal step in the sequence involved generation of a bicyclic oxonium ylide, which rearranges to give the *cis* and *trans* isomers of the oxobicyclo[6.2.1]undecene skeleton, **154a** (*E*) and **154b** (*Z*). The advanced intermediate **154b** (*Z*) was converted to (±)-vigulariol **155** following a short synthetic sequence. The bridged *trans* structure **154a** (*E*) can also serve as a useful starting point for the synthesis of other *cladiellin* natural products **156-158**, displaying vast scope and efficacy for this methodology.



Scheme 1.63

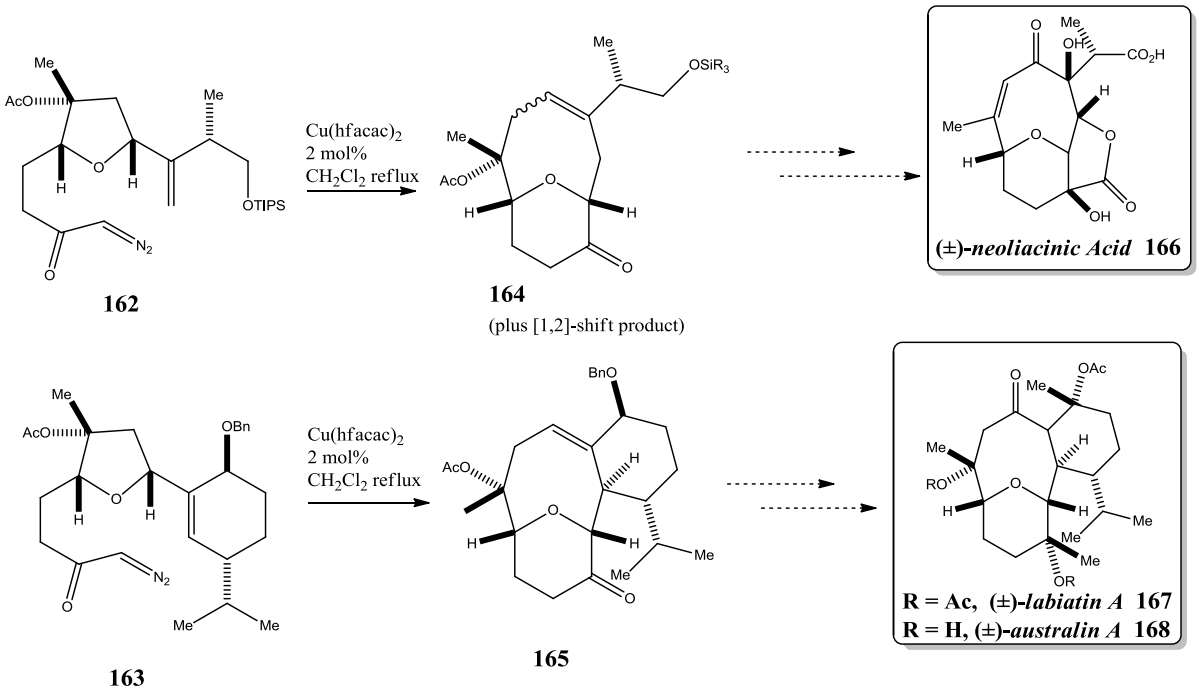
Expanded bridged ethers were prepared by Clark and co-workers *via* rearrangement of catalytically generated bicyclic oxonium ylides (**Scheme 1.64**).[188] Reaction of tetrahydrofuran **159** with Cu(hfacac)$_2$ exclusively provided the bicyclic ether **160** in moderate yield, with *E*-alkene geometry observed. In contrast, $Rh_2(OAc)_4$-catalysed cyclisation of **159** furnished an equal mixture of *E* and *Z* isomers **160** and **161** in low yield.



Scheme 1.64

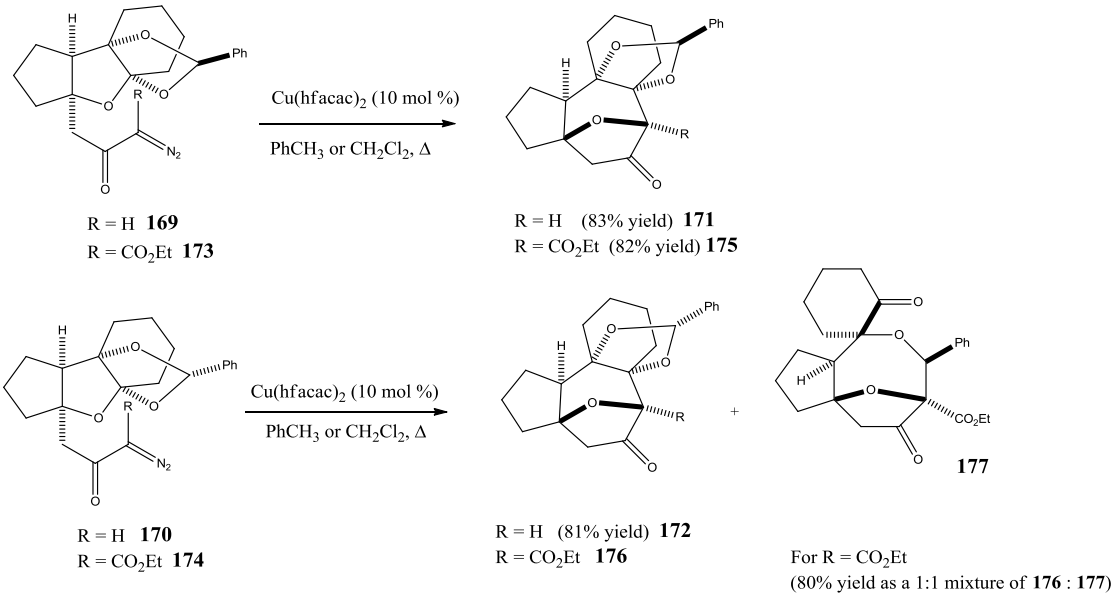
A natural extension of this work has been carried out by Clark in elegant syntheses towards natural products using oxonium ylide formation/rearrangement as a key tool to construct the highly functionalised core structures of (±)-neoliacinic acid **166**, (±)-labiatin A **167** and australin A **168** from related α-diazocarbonyl templates **162** and **163** (**Scheme 1.65**).[189-191] Tandem oxonium ylide formation/[2,3]-rearrangement of **162** and **163** furnished the ring-

expanded oxacycles **164** and **165**, which can be elaborated to generate key synthetic intermediates towards synthesis of the cores of (±)-neoliacinic acid **166**, (±)-labiatin A **167** and (±)-australin A **168**. Copper(II) bis(hexafluoroacetylacetonate) was the catalyst of choice for the α-diazoketone cyclisations, resulting in higher yields and less side products observed.



Scheme 1.65

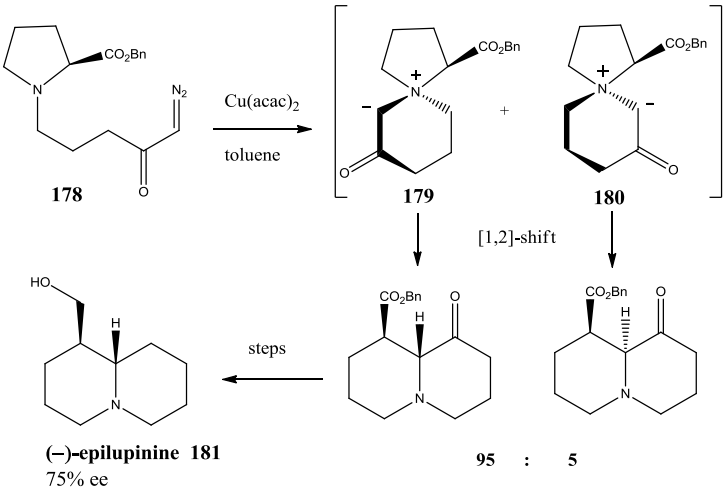
The first example of concomitant oxonium ylide/[1,2]-shift from a heteroatom-containing tetracycle was published by West, the process providing an expedient route to the tigliane-dauphane skeleton (**Scheme 1.66**).[192] The respective α- and β-anomers of both α-diazoketones and α-diazo-β-ketoesters were investigated as substrates for the reaction. Cyclisation of α-diazoketones **169** and **170** in the presence of $Cu(hfacac)_2$ provided a single product in each case, **171** and **172**, the [1,2]-rearrangement proceeding with retention of configuration at the migrating carbon. Substrate **172** was stereoselectively reduced to the corresponding alcohol and X-ray crystal analysis confirmed the configuration assigned. Cyclisations of α-diazo-β-ketoesters **173** and **174** gave rise to the expected [1,2]-shift products **175** and **176**, as well as an unexpected spirocyclic oxacanone product **177**, which was isolated in a 1 : 1 mixture with the rearrangement product **176**. The structure of this unanticipated 8-membered lactone was also confirmed by X-ray diffraction. A suggested explanation for the unexpected ring-expanded product involves fragmentation of either the biradical or zwitterionic intermediate followed by recombination.



Scheme 1.66

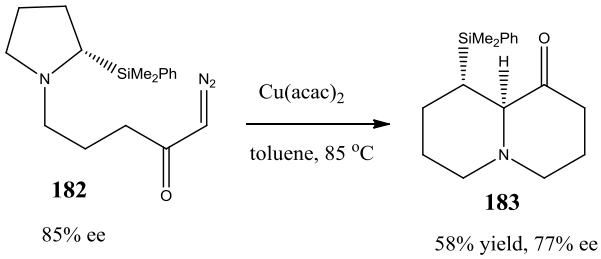
1.5.3.2 Ammonium ylides

The enantioselective synthesis of (–)-epilupinine **181** using tandem ammonium ylide formation/[1,2]-shift methodology has been reported by West and co-workers (**Scheme 1.67**).[193,194] Employment of copper catalysis with α-diazoketone **178** afforded the ammonium ylides **179** and **180**, which are examples of a spiro[4,5]-ylide. Subsequent [1,2]-migration from the spirocyclic ylide generated the quinolizidine framework as a mixture of diastereomers, while functionalisation of the major diastereomer led to the formation of (–)-epilupinine **181** in 75% enantiopurity after a short synthetic sequence.



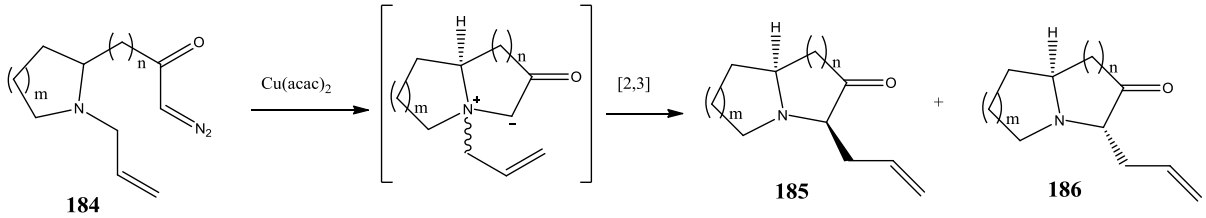
Scheme 1.67

Further work by the same group investigated the use of a silyl group as a replacement for the benzyl ester (**Scheme 1.68**).[195] This silyl-orientated [1,2]-shift provides access to hydroxylated quinazoline systems. Cyclisation of *N*-substituted pyrrolidine α-diazoketone **182** afforded the silylated quinazoline **183** as a single diastereomer in 58% yield and 77% ee.



Scheme 1.68

Clark and co-workers have examined the carbenoid-mediated [2,3]-rearrangement of ammonium ylides using cyclic α-substituted amines containing allyl groups.[196,197] In this work, two distinct categories of substrate were studied; the first type of substrate, **184** (**Scheme 1.69**), involves an α-diazocarbonyl attached to the α-carbon of an *N*-allyl substituted cyclic amine. The second type of substrate, **187**, comprises an *N*-substituted α-diazocarbonyl, where the vinylic group is adjacent to the α-diazocarbonyl functionality (**Scheme 1.70**). In the case of the first substrate type,[197] treatment of **184** with copper(II) acetylacetonate results in tandem ammonium ylide formation/rearrangement to provide the bicyclic products **185** and **186**, facilitating a potentially stereoselective route into pyrrolizidine, indolizidine and quinolizidine alkaloids while enabling high levels of diasterocontrol (**Table 1.11**).

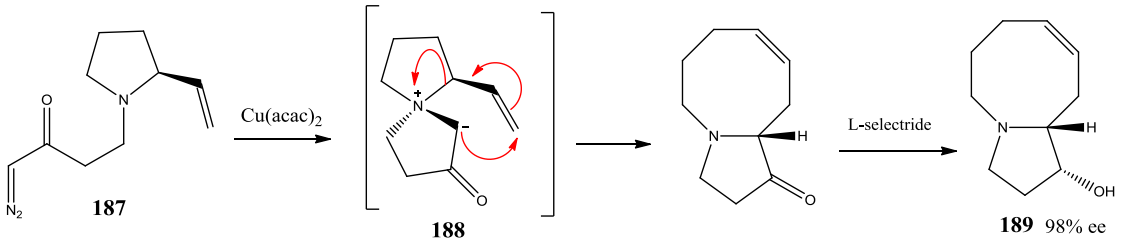


Scheme 1.69

Table 1.11

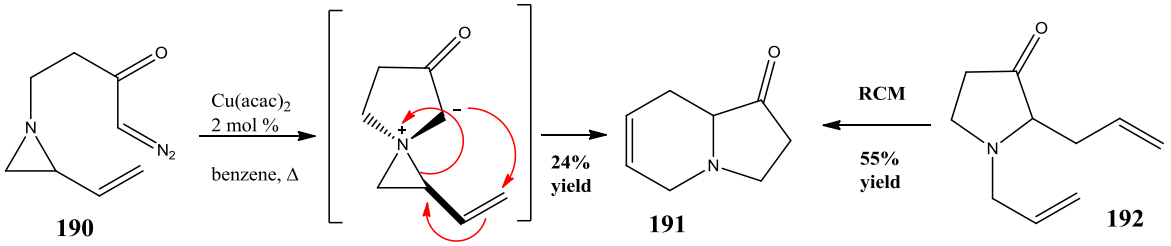
Entry	*n*	*m*	Ratio 185 : 186
1	1	1	100 : 0
2	1	2	100 : 0
3	2	1	3.5 : 1
4	2	2	6.1 : 1

Following the successful formation of bicyclic amines using type 1 substrates, Clark *et al*. also investigated type 2 substrates **187**, where the exocyclic allyl chain subsequently forms part of the ring (**Scheme 1.70**).[196] In this case, the chiral pyrrolidine α-diazoketone **187** was reacted with copper(II) acetylacetonate. The incipient ylide **188** undergoes [2,3]-sigmatropic rearrangement resulting in ring-expansion of the cyclic amine, resulting in loss of the original stereogenic centre and creation of a new stereocentre at the adjacent carbon previously part of the spiro-fused ylide. Reduction of the ring-expanded ketone with L-selectride® resulted in formation of enantiopure alcohol **189**, illustrating a high degree of retention of stereochemical information during the rearrangement of the ylide **188**. Accordingly, this process has developed into a useful route for synthesis of the enantioenriched azabicyclo[6.3.0]undecane skeleton **189**, which is a key structural component of many manzamine alkaloids.



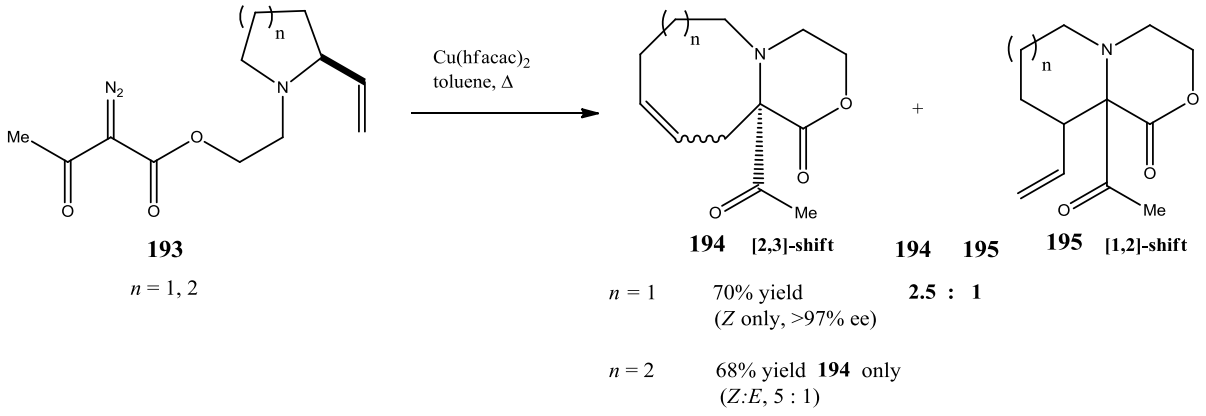
Scheme 1.70

The ammonium ylide formation/ring-expansion strategy of an aziridine substituted α-diazoketone **190** containing a pendant vinyl group has been disclosed by Clark (**Scheme 1.71**).[197] The expected indolizidine **191** was synthesised in modest yield, which the author attributes to the highly unstable nature of the product (decomposed after 24 h). The structure of the indolizidine was confirmed by comparison with analysis from the identical product **191** obtained from ring-closing metathesis (RCM) reaction of diene **192**.



Scheme 1.71

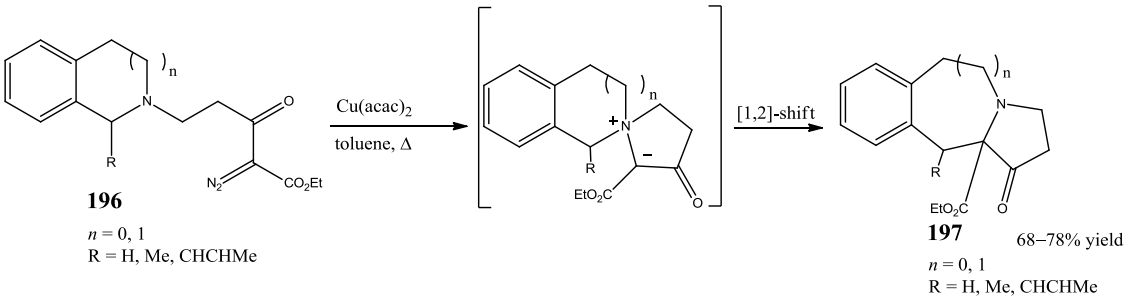
Extension of this methodology to the related α-diazo-β-ketoesters has been demonstrated by McMills and co-workers with particular emphasis on the effect of larger ring sizes on the α-diazocarbonyl cyclisations (**Scheme 1.72**).[198] In the case of vinyl pyrrolidine **193** (*n* = 1), tandem ammonium ylide formation/rearrangement furnished a mixture of [2,3]- and [1,2]-shift products **194** and **195**. Efficient transfer of chirality was observed for the [2,3]-shift product **194**, which was identified as the *Z*-isomer exclusively. Reaction of the vinyl piperidine **193** (*n* = 2) resulted in formation of the [2,3]-rearrangement product **194** only (mixture of *Z* and *E* isomers) and complete absence of the competing Stevens rearrangement product **195**.



Scheme 1.72

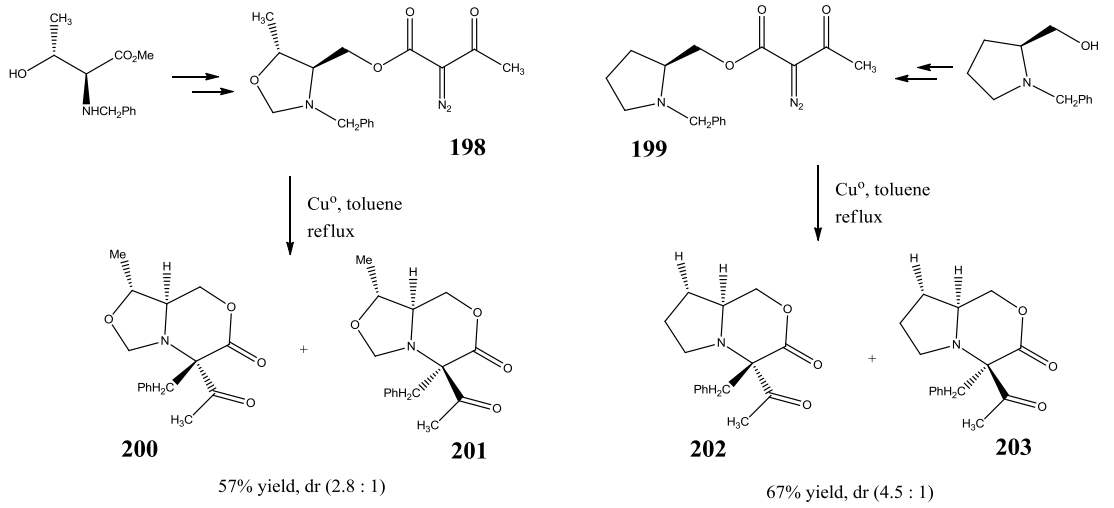
In 1998, a similar method was applied by Padwa in the synthesis of natural products (**Scheme 1.73**).[199] Generation of the copper carbenoid from bicyclic α-diazo-β-ketoesters **196** leads to concomitant spirocyclic ammonium ylide/[1,2]-migration, establishing one carbon ring-

expanded products **197**, which are integral structural components of the cephalotaxine skeleton. All of the reactions gave products arising from migration of the benzylic carbon atom as expected. This strategy was further employed by Padwa *et al.* allowing rapid formation of isoindolo-benzazepines as a core structure of complex polycycles.[200]



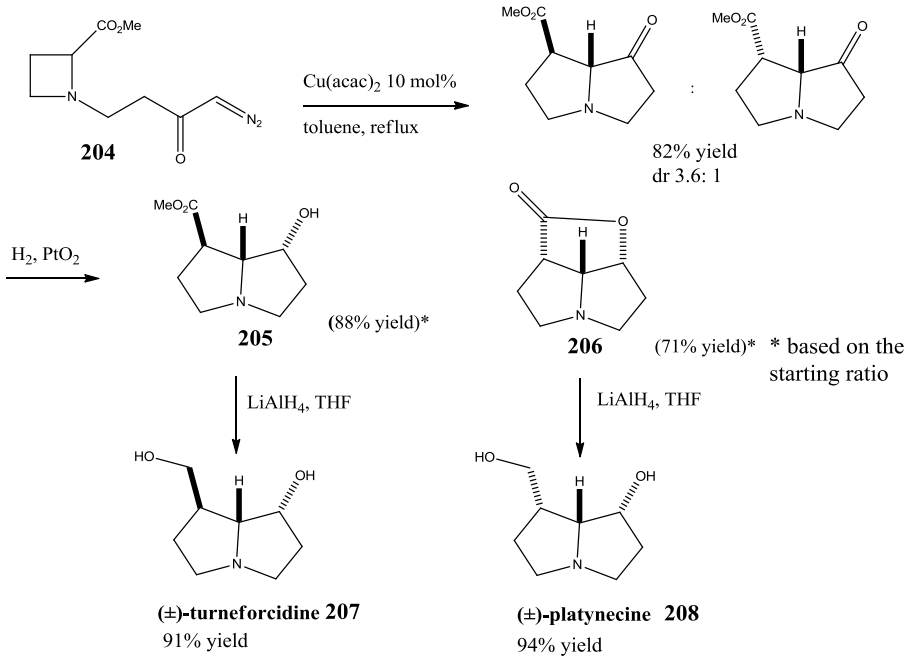
Scheme 1.73

Using an elaborate strategy, West has carried out stereoselective formation of amino α-diazoacetoacetates prepared from readily available chiral amino alcohols (**Scheme 1.74**).[201] Investigations focused on cyclic substrates such as *N*-benzylprolinol and acyclic *N*-benzylthreonine, which was converted to the chiral oxazolidine **198**. The α-diazo-β-ketoesters **198** and **199** were synthesised in high yields and subsequent reaction with copper powder in refluxing toluene furnished the fused bicyclic products **200-203**. These bicyclic products displayed impressive stereoselectivity with a 4.5 : 1 ratio of diastereomers observed for the *N*-benzylprolinol derivatives **202** and **203**. This methodology enables an efficient route to unnatural amino acid derivatives.



Scheme 1.74

Extension of the substrate scope of cyclic ammonium ylides has been provided by West through investigation of ring-expansion reactions of azetidinium ylides, affording a convenient route to pyrrolizidine alkaloids, (±)-turneforcidine **207** and (±)-platynecine **208** (**Scheme 1.75**).[202] Copper-catalysed cyclisation of azetidine-derived α-diazoketone **204** furnished an inseparable mixture of diastereomers in high yield *via* [1,2]-shift of the ylide. The mixture was subsequently hydrogenated to provide hydroxyester **205** and lactone **206**, followed by further reduction using lithium aluminium hydride to give the two natural products **207** and **208** in high overall yields *via* a five-step sequence.



Scheme 1.75

In 2005, Sweeney reported the first examples of sigmatropic rearrangements of a new class of spirocyclic ammonium ylides, ene-*endo*-spiro ylides, in which the alkene moiety is endocyclic.[203] Previous examples by West[193,194] and Clark[196] have examined spiro yildes and ene-*exo* spiro ylides as discussed above (**Figure 1.7**).

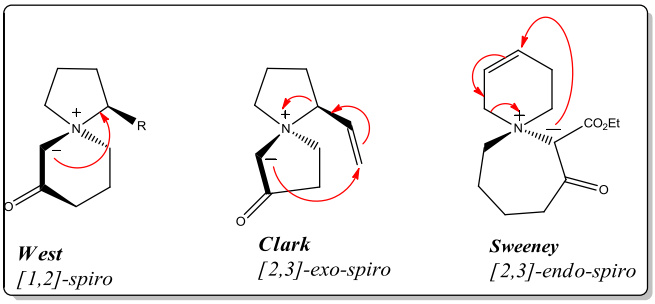
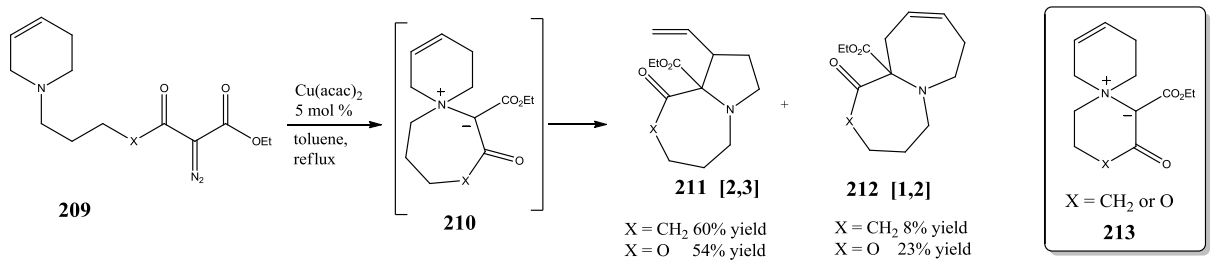


Figure 1.7[203]

The tetrahydropyridine α-diazo-β-ketoesters **209** containing a *N*-tethered diazo moiety were reacted with catalytic $Cu(acac)_2$ to prepare spiro[5,6]-ylide **210** (**Scheme 1.76**). Following rearrangement of the ammonium ylide, the [2,3]-rearrangement products **211** were obtained in good yields (X = CH_2 60%, X = O 54%) with the [1,2]-shift product **212** also observed as a minor component (X = CH_2 8%, X = O 23%). Tetrahydropyridine analogues possessing a shorter carbon linker afforded the corresponding spiro[5,5]-ylides **213** on reaction in the presence of $Cu(acac)_2$. While these shorter-chain analogues displayed similar reaction outcomes, formation of the [1,2]-shift product was slightly favoured for the morpholinone system (X =O, ~1.5 : 1) whereas the piperidinone system (X = CH_2) provided a 1 : 1 mixture of the rearrangement products. Thus, the extra rigidity of the spiro[5,5]-ylides **213** hinders the [2,3]-rearrangement due to conformational inflexibility in the transition state, in contrast to the spiro[5,6]-ylides. This strategy represents an efficient route to pyrroloazepines and provides access to a range of *stemona* alkaloids.

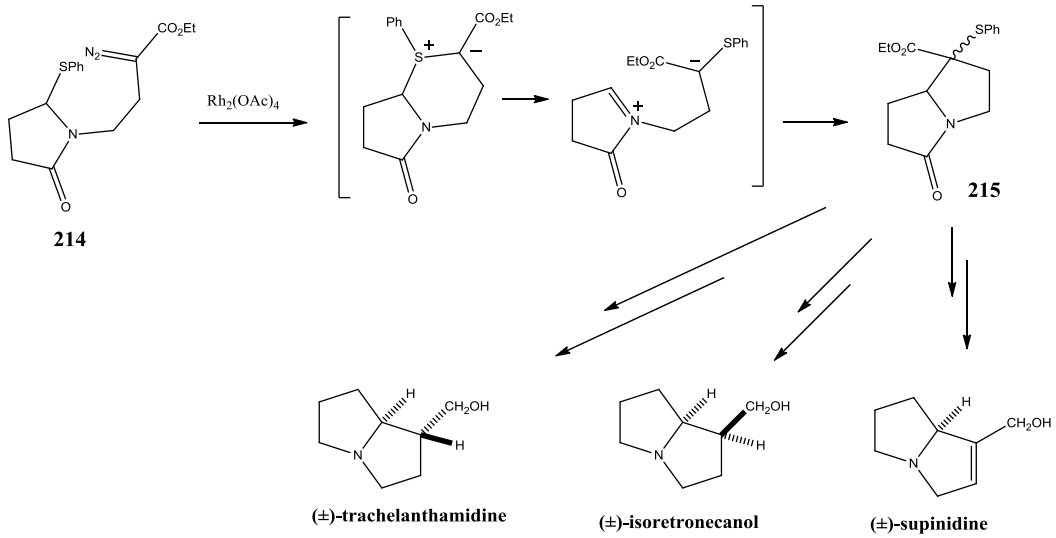


Scheme 1.76

1.5.3.3 Sulfonium ylides

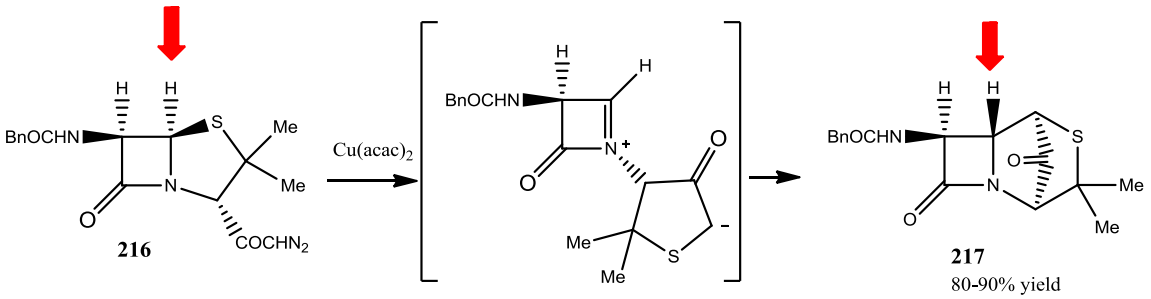
While the intermolecular and intramolecular formation of sulfur ylides has been widely investigated in the preparation of sulfur-containing heterocycles, use of heterocyclic α-diazocarbonyl compounds as viable substrates for these processes has remained largely unexplored.

Honda and co-workers prepared *N*-substituted α-diazoester **214**, possessing an available site for sulfonium ylide formation, attached to the α-carbon to the nitrogen atom.[204,205] An interesting point is that there is also an available carbonyl group on the opposite α-carbon providing an opportunity for carbonyl ylide formation, though this process is not observed. The initially formed sulfonium ylide undergoes a [1,2]-shift process through the acyliminium salt to form the 5-membered bicyclic product **215** in moderate yield. The product **215** has been used as a useful intermediate in the synthesis of three pyrrolizidine alkaloids (**Scheme 1.77**).[204,205]



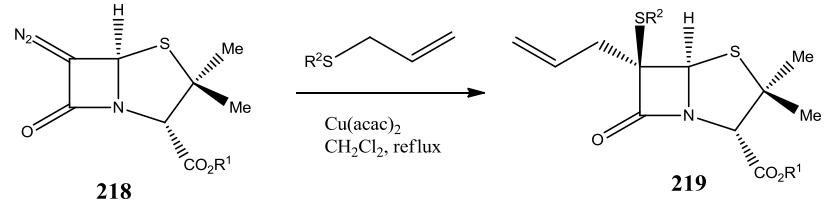
Scheme 1.77

Through further application of this strategy, a penicillin-type substrate **216** was transformed to the bridged ring-expanded product **217** following generation of an iminium ion which facilitates the Stevens rearrangement.[206,207] The author reports the involvement of the iminium ion being consistent with the change in stereochemistry at the bridgehead carbon on the azetidine ring, as illustrated below (**Scheme 1.78**).



Scheme 1.78

Intermolecular sulfonium ylide formation has been applied on a similar penam system. Thomas and co-workers have introduced additional functionality to the parent β-lactam by treatment of **218** with a range of simple allylic sulfides in the presence of copper(II) acetylacetonate (**Scheme 1.79**).[208] The rearrangement products **219** were obtained in high yield while moderate diasterocontrol was observed in the reaction.

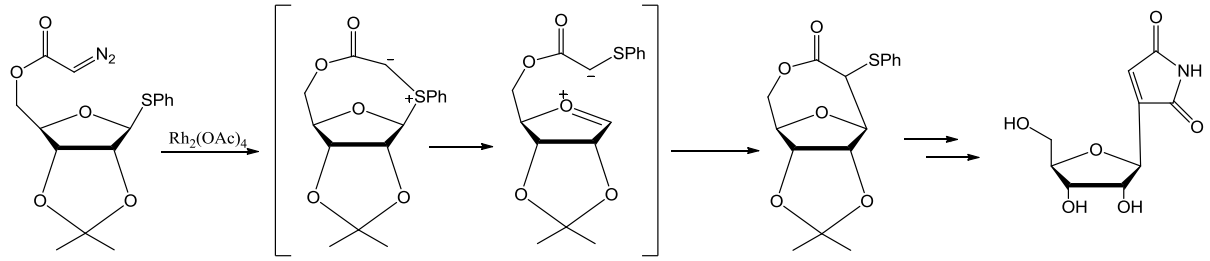


$R^1 = CH_2CCl_3$, CH_2Ph
R^2 = Me, Ph

60–65% yield
dr 80 : 20–87 : 13

Scheme 1.79

Further investigation of the sequential intramolecular sulfonium ylide formation/rearrangement has been explored by Kim, who has utilised this methodology in the formal synthesis of (+)-showdomycin (**Scheme 1.80**).[209] The tetrahydrofuran substituted α-diazocarbonyl compound **220** afforded the cyclic sulfonium ylide on treatment with rhodium(II) acetate. In this case, the sulfonium ylide rearranges to generate the lactone **221** in 48% yield. Further synthetic embellishment of the lactone **221** provided (+)-showdomycin **222** after a short synthetic sequence.



220

221
48% yield

(+)-showdomycin 222

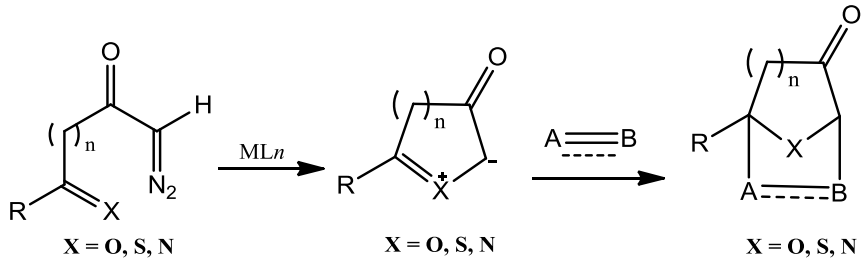
Scheme 1.80

Thus, reaction of α-diazocarbonyl compounds with a heteroatomic Lewis base (O, S, N) results in the formation of "onium" ylides. While these ylide species contain a common general structure, the rearrangement pathways vary depending on the particular structural features of the ylide substrate.

1.5.3.4 Carbonyl, thiocarbonyl and azomethine ylides

1.5.3.4.1 Introduction

Carbonyl ylides are efficiently trapped by dipolarophiles in 1,3-dipolar cycloaddition reactions generating oxygen heterocycles, with the corresponding thiocarbonyl and azomethine ylides providing access to sulfur and nitrogen heterocycles respectively. A general example of the intermolecular cycloaddition of carbonyl, thiocarbonyl and azomethine ylides is shown below (**Scheme 1.81**). These ylides can undergo both intermolecular and intramolecular cycloadditions with a general representation of inter- and intramolecular [3+2]-cycloadditions illustrated below (**Figure 1.8**).



Scheme 1.81: Intermolecular 1,3-dipolar cycloadditions of carbonyl, thiocarbonyl and azomethine ylides (adapted from Padwa)[210]

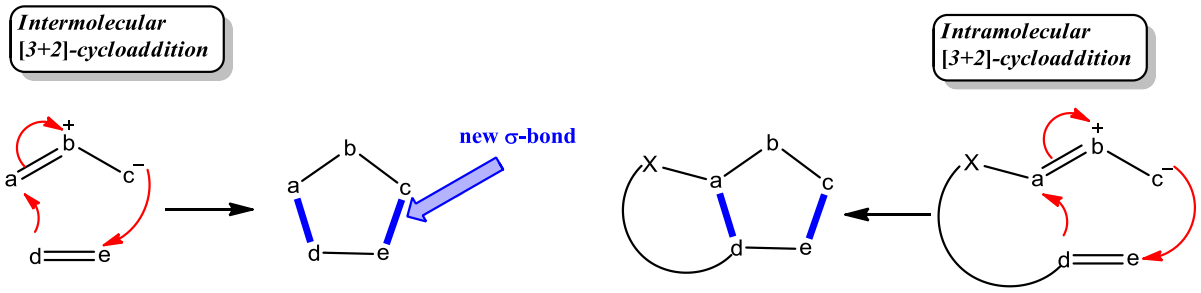


Figure 1.8: Inter- and intramolecular 1,3-dipolar cycloadditions

Cycloaddition reactions feature prominently in synthetic organic chemistry with Diels-Alder/[4+2]- and 1,3-dipolar/[3+2]-cycloadditions among the most well-renowned. These synthetic routes have proven very useful in the synthesis many natural and unnatural products by increasing molecular complexity from simple precursors to more complex polycyclic systems in a single synthetic operation. Since the pioneering work of Huisgen and co-workers in the early 1960's,[211-213] 1,3-dipolar cycloaddition has developed into a powerful synthetic tool for the rapid assembly of five-membered heterocyclic rings in a formal [3+2]-cycloaddition. The 1,3-dipole is composed of 4π electrons delocalised over three atoms and this reacts with a 2π electron component, a dipolarophile, to generate the cycloadduct. In this concerted pericyclic reaction, redistribution of the electrons of the π-bonds results in the generation of two new σ-bonds, as illustrated in blue above (**Figure 1.8**).

Morevover, further structural modification of the cycloadducts presents access to a range of cyclic or acyclic derivatives, serving as versatile scaffolds for the preparation of natural products and related analogues. Another notable feature of this methodology is that it facilitates the installation of multiple stereocentres to the heterocyclic ring in a one-step process.[214] Relative stereocontrol in the 1,3-dipolar cycloaddition arises from the geometry of the dipole and the dipolarophile, proceeding with retention of configuration in the ensuing cycloadducts, while the topography (*endo* or *exo*) of the cycloaddition is also significant.[214] In

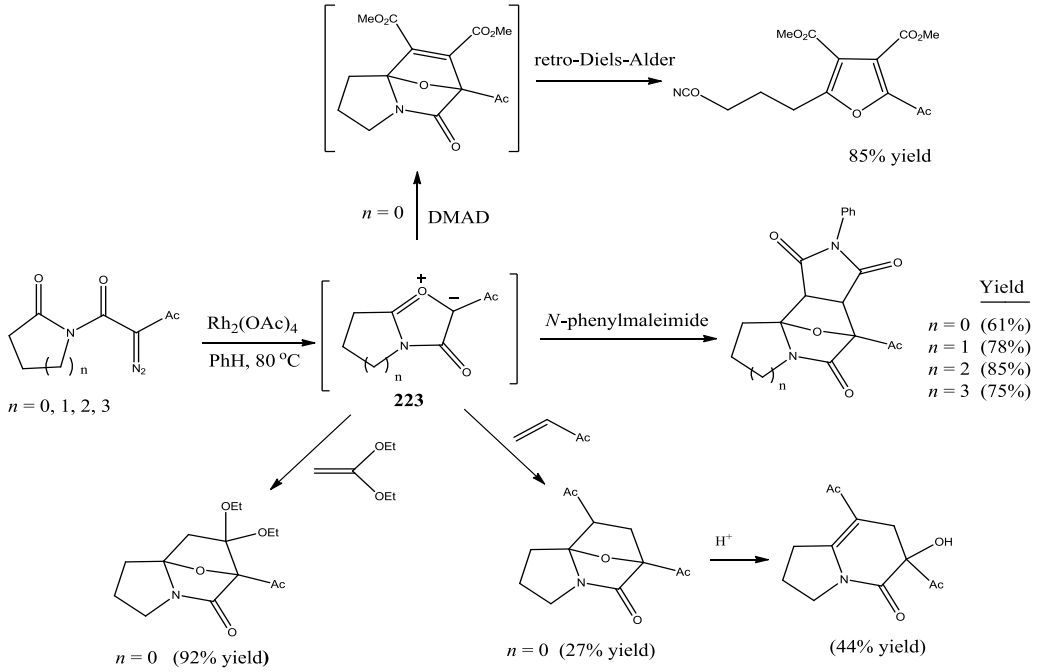
this section, both inter- and intramolecular 1,3-dipolar cycloadditions of carbonyl ylides are discussed, while intermolecular cycloadditions of thiocarbonyl and azomethine ylides are also examined. Two comprehensive books capturing the major highlights of the broad chemistry of 1,3-dipoles have been published by Padwa.[214-216]

1.5.3.4.2 Carbonyl ylides

1.5.3.4.2.1 Intermolecular 1,3-dipolar cycloadditions of carbonyl ylides

Early studies by Ibata and co-workers amply demonstrated the utility of this approach using the rhodium(II)-catalysed reaction of carbonyl ylides derived from phenyl α-diazoketones in the presence of various dipolarophiles.[217-222] Following this, Padwa spearheaded the widespread application of this strategy for the construction of highly-substituted oxacyles as sub-units of polycyclic systems.

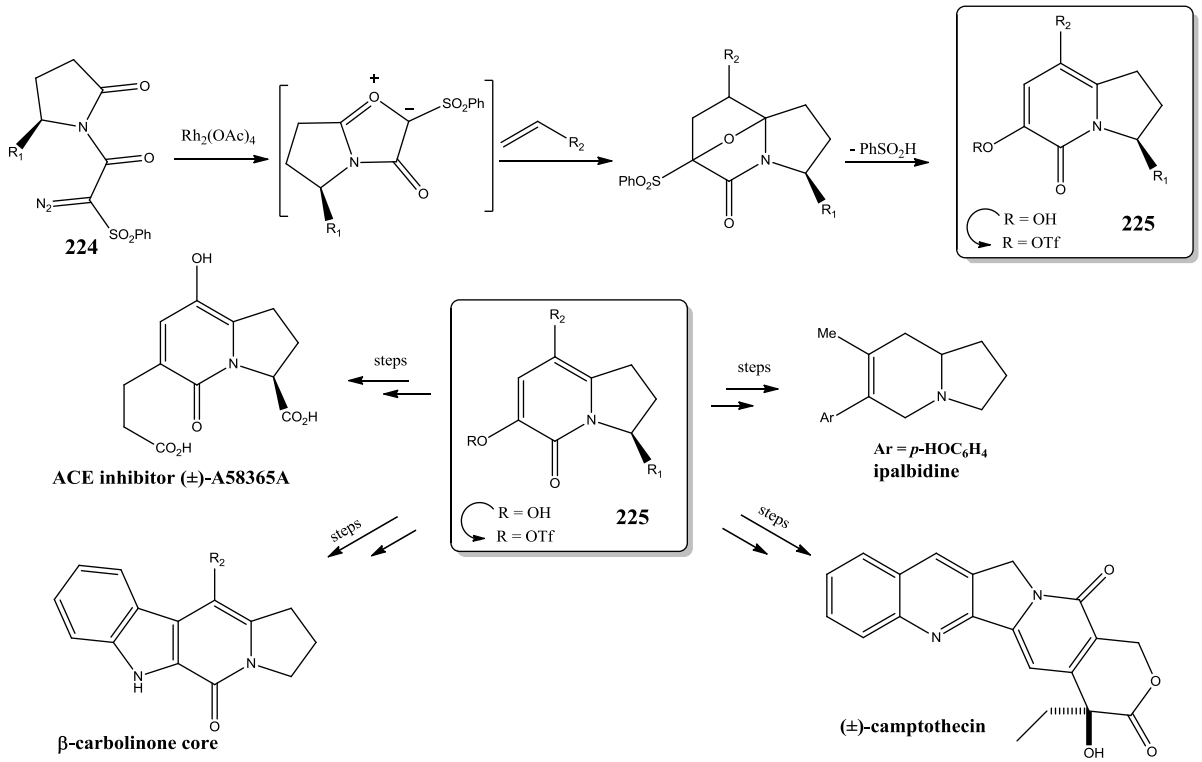
The transition metal-mediated transformations of certain diazo imides afford a special class of carbonyl ylides, termed isomünchnones, with the analogous sulfur-containing compounds giving rise to thioisomünchnones. These mesoionic ring systems are the cyclic equivalent of a carbonyl ylide or thiocarbonyl ylide and can undergo 1,3-dipolar cycloaddition. Noteworthy characteristics of these cyclic ylides include that they exhibit aromatic character and cannot be drawn satisfactorily by normal covalent structures;[223] instead they are best represented as hybrids of all possible charged species. Padwa and co-workers employed bicyclic isomünchnones of type **223** in 1,3-dipolar cycloadditions with a variety of dipolarophiles such as *N*-phenylmaleimide (NPM), dimethylacetylene dicarboxylate (DMAD), diethyl ketene acetal and vinyl acetate.[224,225] The expected cycloadducts were formed in most cases, with the notable formation of a furan isocyanate *via* retro-Diels-Alder reaction from the cycloaddition with DMAD (**Scheme 1.82**).



Scheme 1.82

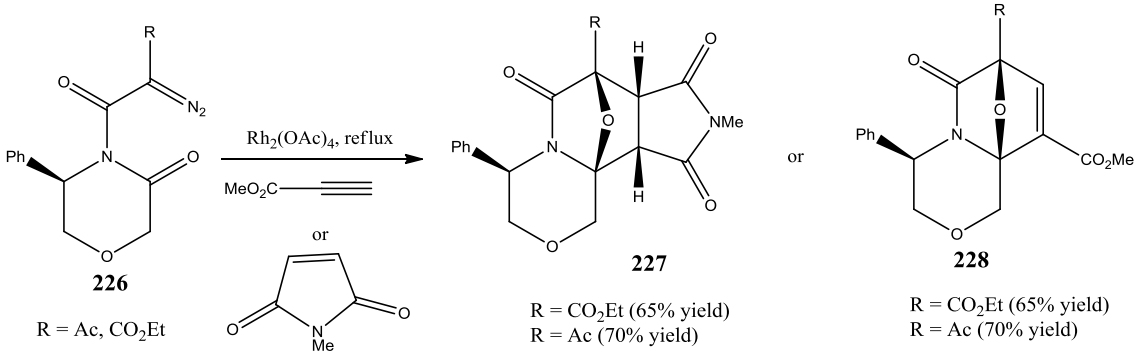
Padwa has expanded this protocol through replacement of the acetyl group with a strongly electron-withdrawing phenylsulfonyl group.[225] Following rhodium(II)-mediated cyclisation of α-diazo-β-ketosulfone **224**, the ensuing isomünchnone ylide was trapped with an appropriate dipolarophile affording the cycloadduct. The newly-formed ring readily opens with loss of

benzenesulfinic acid to give the pyridone **225**, a useful precursor, providing access to a variety of indolizidine alkaloids by modification of the ring and a series of functional group transformations (**Scheme 1.83**). The formation of a triflate from the C–6 hydroxyl group was a vital step in ensuring that a range of cross coupling strategies can be implemented. This strategy led to the synthesis of alkaloids (−)-A58365A,[226,227] (±)-ipalbidine[228] and β-carbolinone[229] by Padwa. This methodology has been employed by Greene and co-workers in the synthesis of racemic camptothecin (**Scheme 1.83**).[230,231]



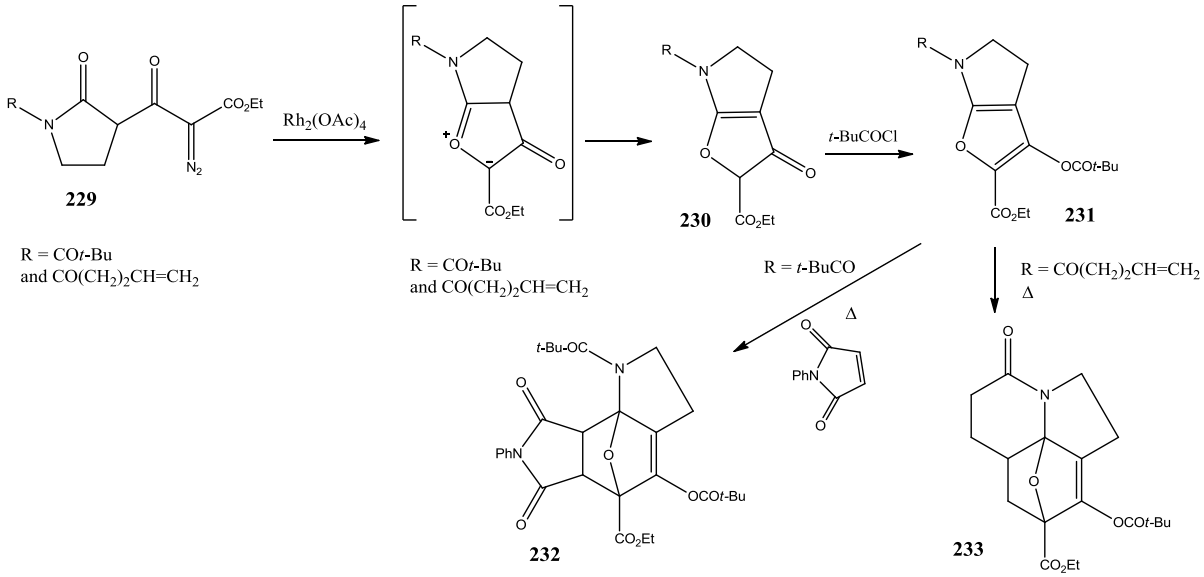
Scheme 1.83

Some interesting chiral templates for sequential isomünchnone formation/cycloadditon have been reported by Harwood *et al*. using a substituted morpholine-type precursor, derived from phenylglycinol.[232,233] Reaction of α-diazoester **226** with rhodium(II) acetate while heating under reflux generated the expected carbonyl ylide, while subsequent cycloaddition with methyl propiolate or *N*-phenylmaleimide delivered the cycloadducts **227** or **228** in good yields (**Scheme 1.84**). The cycloadducts obtained arise from an *endo* addition of the dipolarophile to the less hindered α-face of the carbonyl ylide, with some β-face addition product featuring *exo* selectivity also isolated. Initial studies with maleimides were followed by studies with mono- and disubstituted acetylenic compounds as dipolarophiles furnishing similar results for cycloadducts obtained.



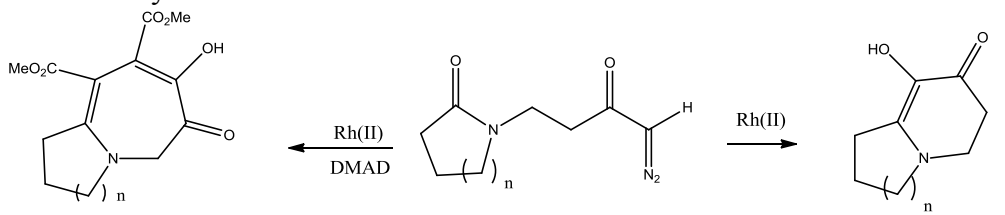
Scheme 1.84

An unusual 1,4-hydrogen shift was identified by Padwa during initial model studies of possible cycloaddition templates derived from **229** (**Scheme 1.85**).[234] It was observed that formation of furanone **230** *via* 1,4-hydrogen transfer proceeded faster than either inter- or intramolecular cycloaddition. This property was later exploited by Padwa to generate bicyclic furan derivative **231** by acylation of **230**, followed by an intermolecular Diels-Alder cycloaddition of the furan moiety with *N*-phenylmaleimide to afford the cycloadduct **232**. Intramolecular Diels-Alder cycloaddition is also facilitated through tethering of an allyl group to the cyclic amine, followed by 1,4-hydrogen transfer, acylation and cycloaddition to furnish the bridged tricyclic cycloadduct **233**. This methodology enables a three-step approach to prepare polysubstituted *amaryidacae* alkaloids.[235]



Scheme 1.85

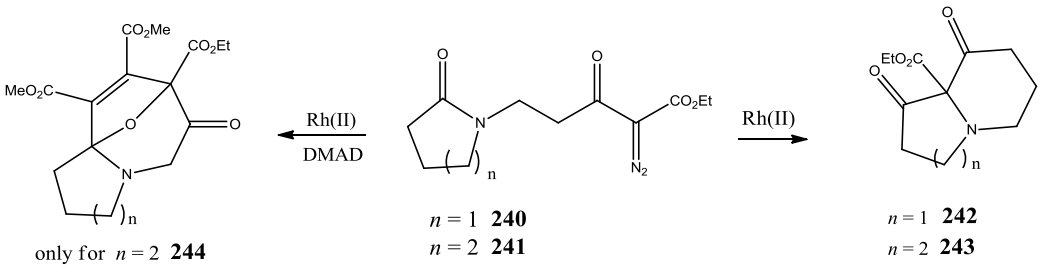
Building on earlier work of similar pyrrolidone- and piperidone-tethered α-diazocarbonyl compounds, Padwa has extended the aliphatic linker-chain on the substituted cyclic amine, increasing the distance of the diazo group from the potential site of carbonyl ylide formation (**Scheme 1.89**).[210] Reactions of α-diazoketones **234** and **235** in the presence of rhodium(II) acetate gave the corresponding bicyclic hydroxyl compounds **236** and **237** possessing the desired indolizidine skeleton. Interestingly, on carrying out reaction of pyrrolidinone **234** in the presence of DMAD, the azocinone cycloadduct **238** was generated in addition to hydroxyindolizinone **236**, while in the case of α-diazoketone **235**, the cycloadduct **239** was provided exclusively.



Scheme 1.86

In the same work, additional investigations were carried out using related α-diazo-β-ketoesters **240** and **241**, which underwent similar reaction pathways to α-diazoketones **234** and **235**. Rhodium(II)-mediated transformation of **240** generated solely the indolizidone **242** whereas reaction of **241** yielded both indolizidone **243** and cycloadduct **244** (**Scheme 1.87**).[210]

It is postulated by Padwa that the formation of the indolizidone arises *via* initial formation of a carbonyl ylide which collapses to generate an epoxide as a transient intermediate. The epoxide subsequently isomerises to produce the stable product, though in the case of the α-diazo-β-ketoesters, it is thought the formation of the product may involve the intermediacy of an aziridinium ion.[210]



Scheme 1.87

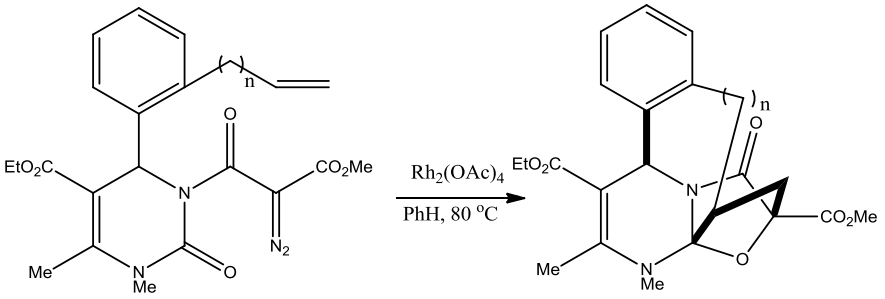
1.5.3.4.2.2 Intramolecular 1,3-dipolar cycloadditions of carbonyl ylides

The intramolecular 1,3-dipolar cycloaddition of carbonyl ylides is an efficient, concise route to form polycyclic systems leading to the formation of key frameworks for a vast array of natural products. A notable feature of this strategy is the presence of an alkene group in the compound either as:

(i) a pendant alkene which subsequently reacts with the newly-formed ylide, or

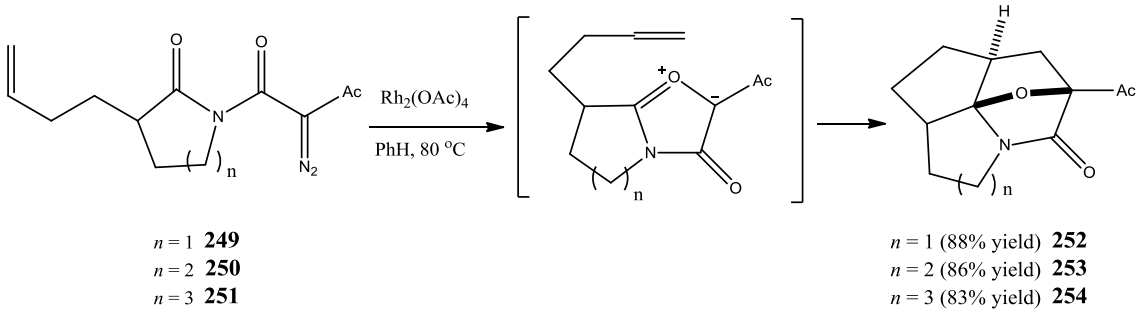
(ii) part of a heterocyclic ring system in close proximity to the available ylide.

Kappe *et al*. have synthesised tetracyclic dihydropyrimidine derivatives by intramolecular cycloadditions of type (i) α-diazo-β-ketoesters **245** and **246** (**Scheme 1.88**).[236] Treatment with rhodium(II) acetate resulted in the initial formation of an isomünchnone ylide, followed by concomitant trapping of the ylide by the pendant alkene. The structures of the cycloadducts **247** and **248** were confirmed by X-ray crystallography.



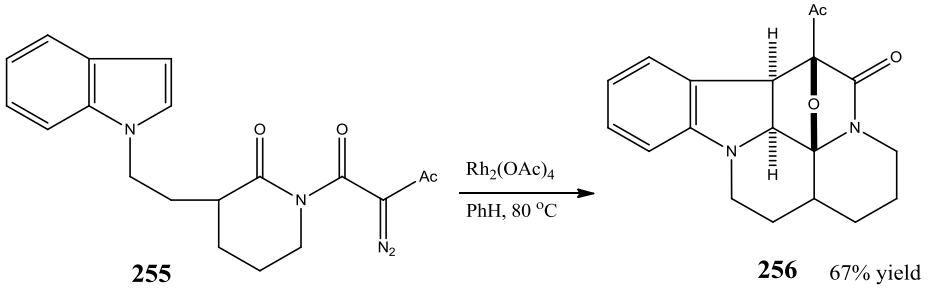
Scheme 1.88

Padwa has employed both type (i) and type (ii) substrates towards the formation of complex polycyclic systems.[237] For the substituted α-diazoimide compounds **249-251** (**Scheme 1.89**), type (i), the isolated π-bond of the alkene is intercepted by the *in situ* generated isomünchnones upon cyclisation in the presence of rhodium(II) acetate, resulting in bridged tricyclic products **252-254** in high yields.



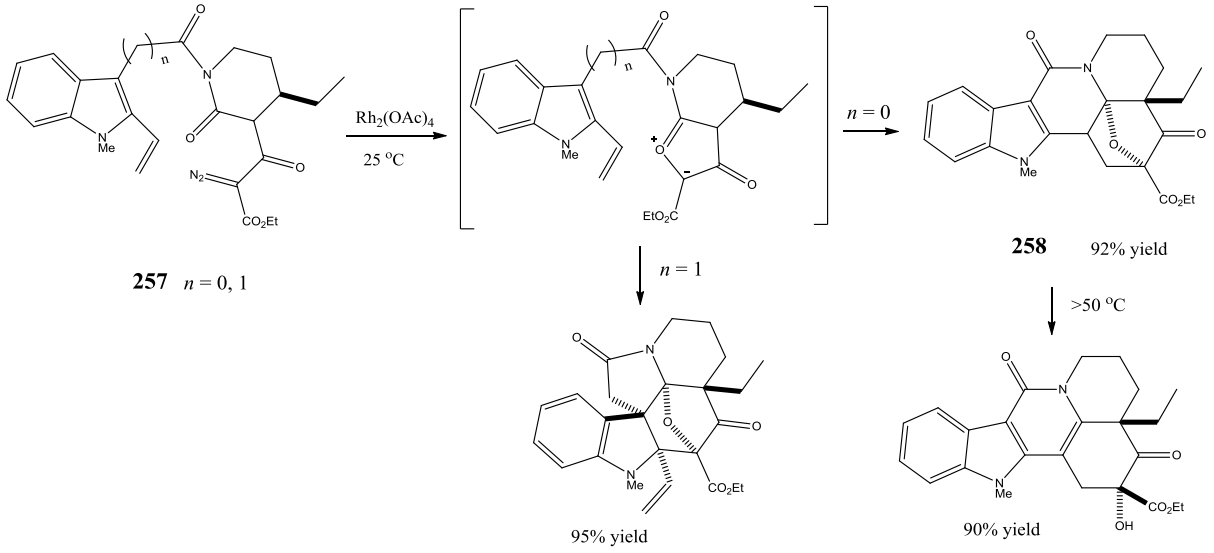
Scheme 1.89

An example of type (ii) systems involves the double bond of the indole ring inducing intramolecular cycloaddition by reaction with the isomünchnone 1,3-dipole.[238] Rhodium(II) acetate-catalysed reaction of **255** afforded the desired cycloadduct **256** as a single diastereomer in good yield (**Scheme 1.90**).



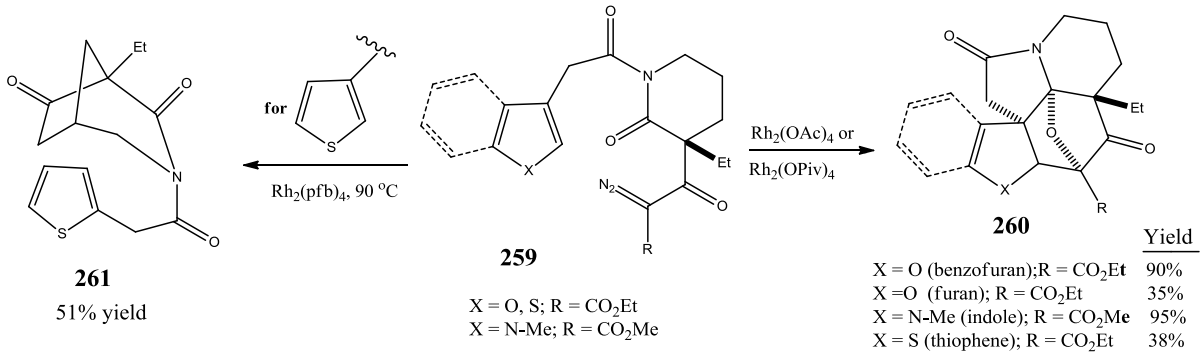
Scheme 1.90

Investigation of [3+2]-cycloadditions of 'push-pull' dipole systems have been carried out by Padwa and co-workers employing a rhodium(II)-mediated domino cyclisation/cycloaddition approach.[239] Rhodium(II)-catalysed reaction of diazoimide **257** (n = 0) containing a tethered vinyl group provided the carbonyl ylide, which was trapped by the neighbouring vinyl group to afford the azapolycyclic product **258** in excellent yield (**Scheme 1.91**). Interestingly, reaction of the higher homogoue (n = 1) provided the cycloadduct arising from cycloaddition of the transient carbonyl ylide across the indole 2,3-π-bond in preference to the tethered vinyl group.



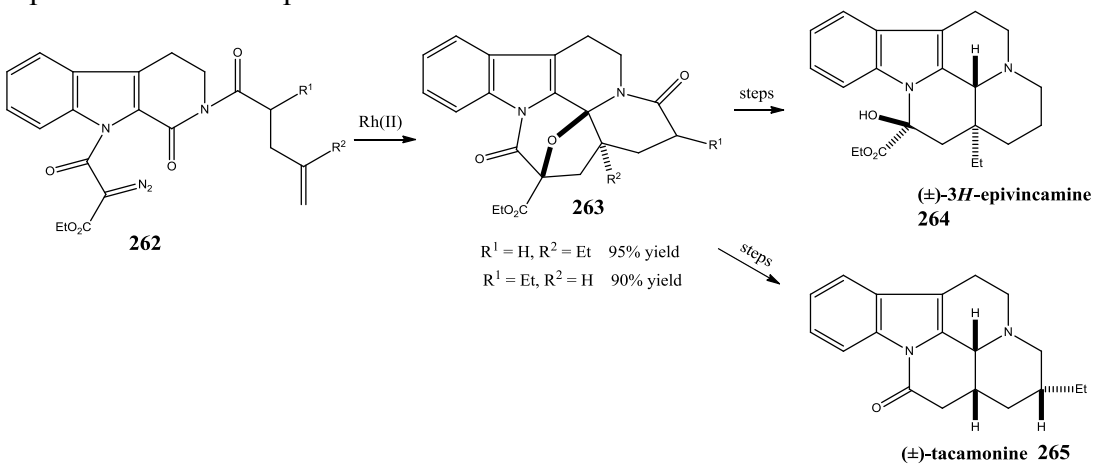
Scheme 1.91

Related heterocycles such as furans, benzofurans, thiophenes and *N*-methyl substituted indole of type **259** were also investigated by Padwa and the polycyclic cycloadducts **260** were prepared in high yields from the bicyclic precursors and moderate yields from the monocyclic counterparts (**Scheme 1.92**).[240] Surprisingly, treatment of the thiophene analogue with electron-deficient $Rh_2(pfb)_4$ catalyst formed bridged lactam **261**, arising from C–H insertion into C(5)–H of the lactam ring followed by an unusual loss of the ester at the site of insertion.[241]



Scheme 1.92

In 2008, Padwa and England reported an easily accessible route to *vinca* and *tacaman* alkaloids using a rhodium(II)-mediated tandem cyclisation/cycloaddition strategy (**Scheme 1.93**).[242] Once again, the pivotal step consists of an intramolecular [3+2]-cycloaddition of the carbonyl ylide and the pendant alkene establishing the bridged pentacyclic skeleton of the natural product in excellent yield. Following an initial feasibility study on a related substrate, the α-diazo-β-ketoester precursors **262** were formed in high yields. Treatment of **262** with $Rh_2(OAc)_4$ provided the bridged cycloadducts **263**, which after a short sequence of steps were functionalised to afford (±)-3*H*-epivincamine **264** and (±)-tacamonine **265** respectively. Padwa has extended the breadth of the domino dipole formation/cyclisation sequence with the formation of complex natural products such as (±)-aspidophytine,[243] as well as synthetically useful precursors to the kopsifoline framework.[244]

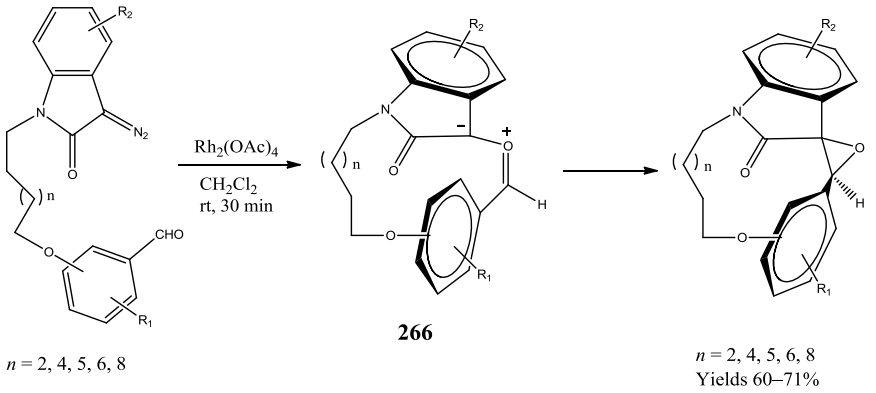


Scheme 1.93

1.5.3.4.2.3 Miscellaneous reactions of carbonyl ylides

In 2011, Muthusamy and co-workers disclosed diastereoselective synthesis of macrocycles incorporating spiro-indolooxiranes (**Scheme 1.94**).[245] The key step in this synthesis involves the formation of a carbonyl ylide from rhodium(II)-mediated reaction of the α-diazocarbonyl compound and subsequent reaction with pendant aldehyde. The proposed mechanism

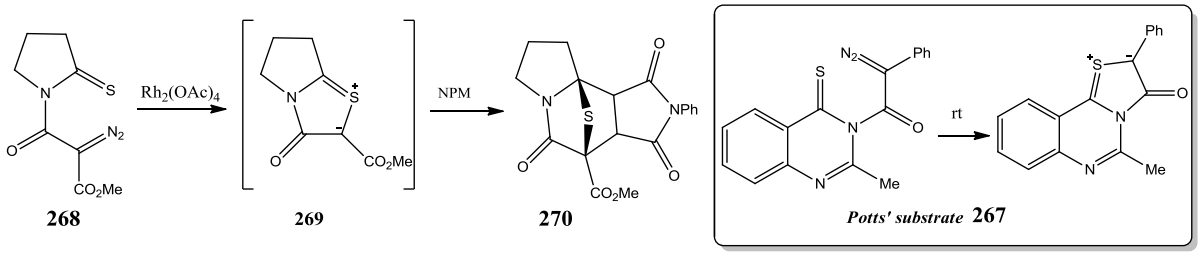
comprises a thermal conrotatory electrocyclisation of the ylide intermediate **266** to yield the desired macrocyclic epoxides. Using this methodology, 13–19-membered macrocycles were synthesised in good yields with complete diastereocontrol.



Scheme 1.94

1.5.3.4.3 Thiocarbonyl ylides

The first preparation of thioisomünchnones from α-diazocarbonyl precursors was reported by Potts and Murphy by *in situ* formation of a *N*-substituted diazothioamide and subsequent formation of the mesoionic species **267** upon stirring at room temperature.[246] Using this methodology, a range of thioisomünchnones were formed in high yields but curiously, no subsequent reactions were carried out by Potts on these systems. Interestingly, these compounds were isolated as crystals and fully characterised, indicating the highly stable nature of the thiazolium mesoionic systems. Going one step further, Padwa carried out reactions of methyl 2-diazo-3-oxo-3-(2-thioxopyrrolidin-1-yl)propanoate **268**, providing the thioisomünchnone **269**, which was trapped by *N*-phenylmaleimide to furnish the sulfur-bridged cycloadduct **270** (**Scheme 1.95**).[247] This strategy was further employed by Padwa and co-workers toward other annelated thiophene derivatives.[248-250]

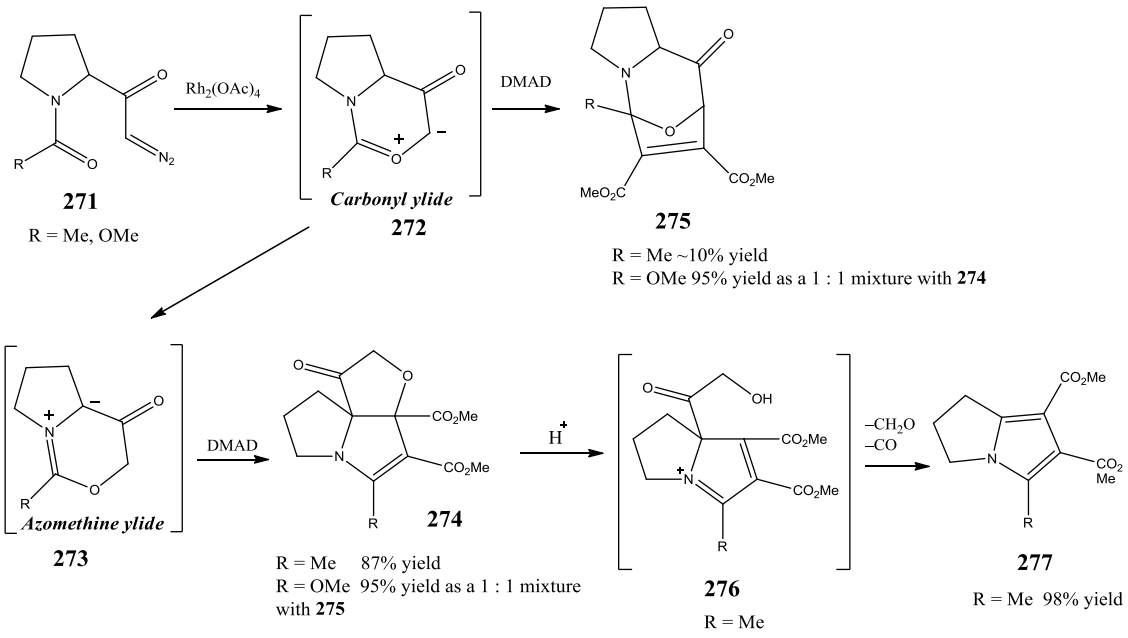


Scheme 1.95

1.5.3.4.4 Azomethine ylides

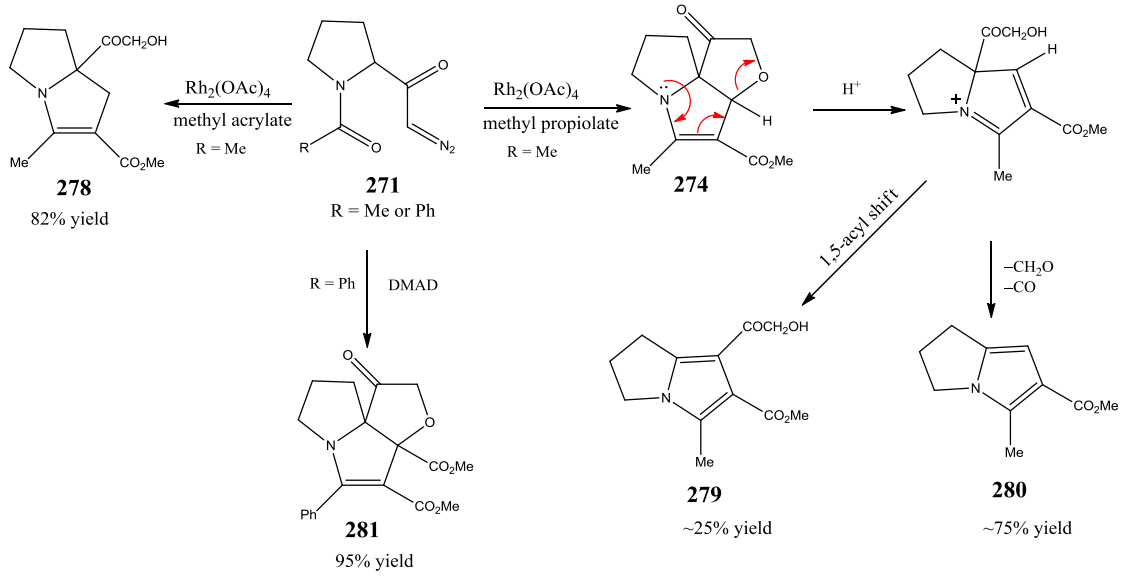
Azomethine ylides can be prepared by a variety of routes including deprotonation of iminium salts, ring-opening of aziridines and desilylation of α-silyl imines; these reactive intermediates can be conveniently trapped by reaction with dipolarophiles and characterised as the analogous cycloadducts. Moreover, an important intrinsic property of carbonyl ylides is their ability to undergo rearrangement to give other 1,3-dipoles, namely azomethine ylides. This process has been described by Padwa as a "dipole cascade" and expedites an efficient method for the preparation of nitrogen-containing heterocycles. Cyclisation of α-diazoketone **271** using rhodium(II) acetate provided carbonyl ylide **272**, which subsequently underwent isomerisation to the more thermodynamically stable azomethine ylide **273**.[251] Ensuing 1,3-

dipolar cycloaddition and rearrangement afforded the tricyclic pyrrolizine **274** in 87% yield (R = Me) while cycloaddition of the initially formed carbonyl ylide **272** with DMAD was also observed, generating the compound **275** in 10% yield (R = Me). In contrast, introduction of a methoxy substituent to the tethered amine provided an inseparable 1 : 1 mixture of cycloadducts **274** and **275** in 95% yield following reaction of carbomethoxy α-diazoketone with $Rh_2(OAc)_4$ (**Scheme 1.96**). The tricyclic pyrrolizine **274** (R = Me) fragmented on exposure to acid *via* **276** to produce pyrrole derivative **277** in 98% yield.



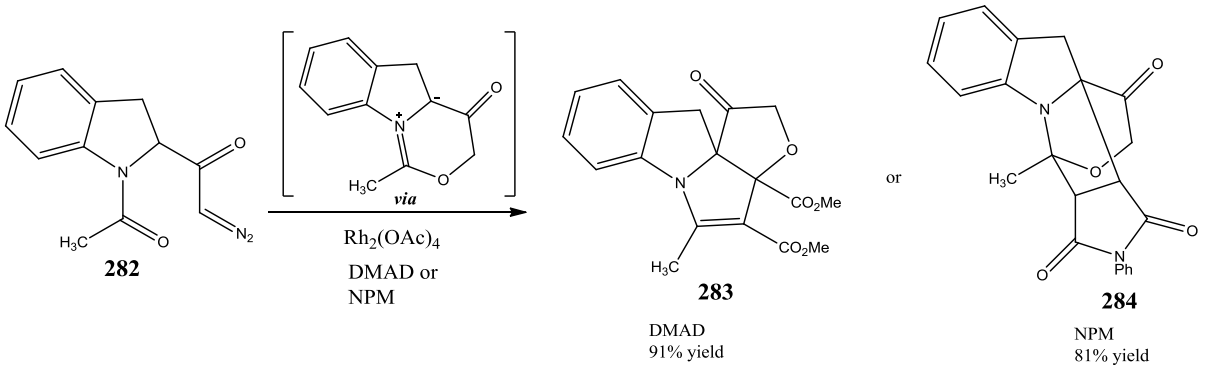
Scheme 1.96

This reaction has also been attempted employing other dienophiles in the cycloaddition.[252] Reaction of α-diazoketone **271** (R = Me) with methyl acrylate or methyl propiolate provided the products **278**, **279** and **280** (**Scheme 1.97**). Treatment of the intermediate **274** with acid resulted in the formation of an iminium ion, which could undergo a 1,5-acyl shift to yield pyrrole **279** or simultaneously lose CH_2O and CO to afford pyrrole **280**. The products were isolated in a 1 : 3 ratio. Replacement of the *N*-acyl with an *N*-benzoyl unit and subsequent rhodium-catalysed cycloaddition with DMAD resulted in formation of the azomethine-derived adduct **281**, which was isolated in 95% yield.



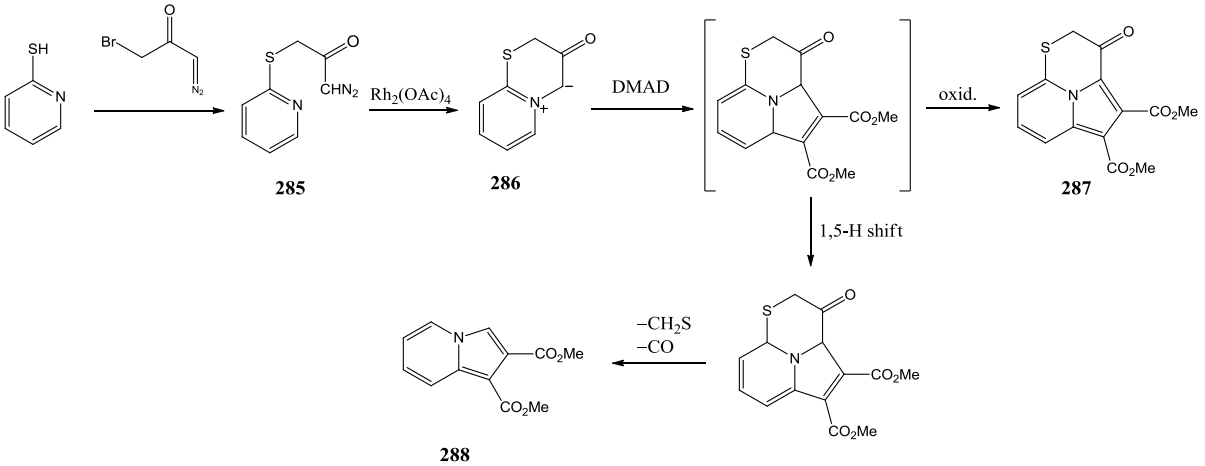
Scheme 1.97

Padwa has investigated if the corresponding indolyl α-diazoketone **282** would react in a similar manner to the pyrrole substituted derivative **271** (**Scheme 1.98**).[252] Reaction of the metallocarbenoid from **282** with the adjacent carbonyl group resulted in a dipole rearrangement to provide the azomethine ylide, followed by reaction with dipolarophiles DMAD or *N*-phenylmaleimide. In each case, the azomethine-based cycloadducts **283** and **284** were generated in high yields, though a 1,3-alkoxy shift was observed for the cycloadduct arising from DMAD to afford tetracycle **283**.



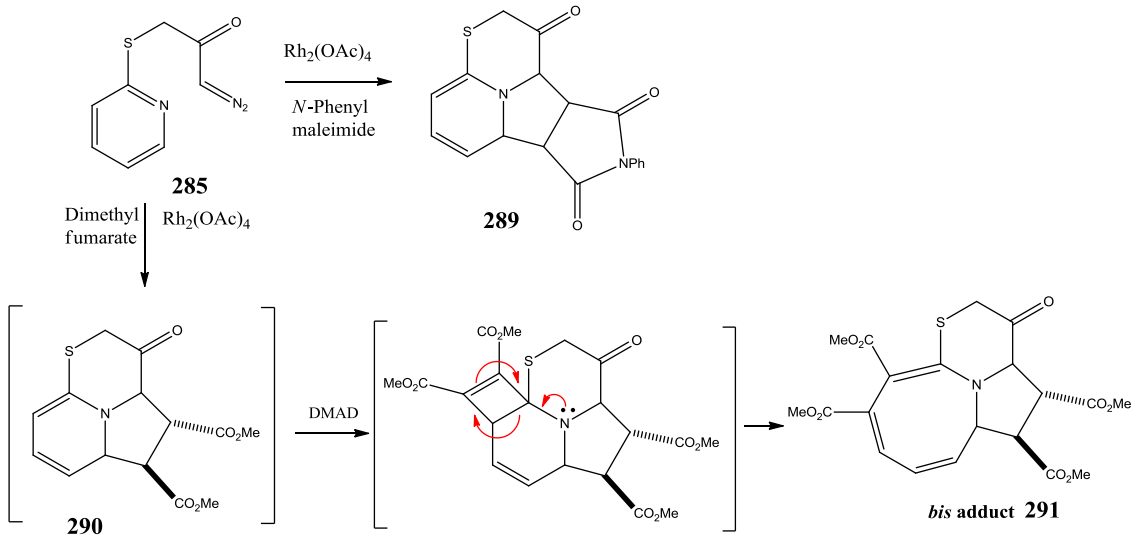
Scheme 1.98

In 1993, Padwa and co-workers carried out cycloadditions of azomethine ylides generated from pyridine α-diazocarbonyl substrates.[253] The α-diazoketones possessed a heteroatomic linker and were prepared by reaction of 1-bromo-3-diazopropan-2-one with a pyridinethiol or hydroxypyridine. The pyridinium/azomethine ylides underwent typical cycloaddition chemistry to afford cycloadducts with dipolarophiles such as dimethyl fumarate, DMAD and *N*-phenylmaleimide. Transition metal-catalysed transformation of α-diazoketone **285** afforded the azomethine ylide **286**, which subsequently underwent dipolar cycloaddition with DMAD to provide the two cycloadducts **287** and **288**. Tricyclic compound **287** arose from oxidation of the precursor, whereas **288** originates from 1,5-hydrogen shift of the initially formed cycloadduct, followed by loss of CH_2S and CO (**Scheme 1.99**).



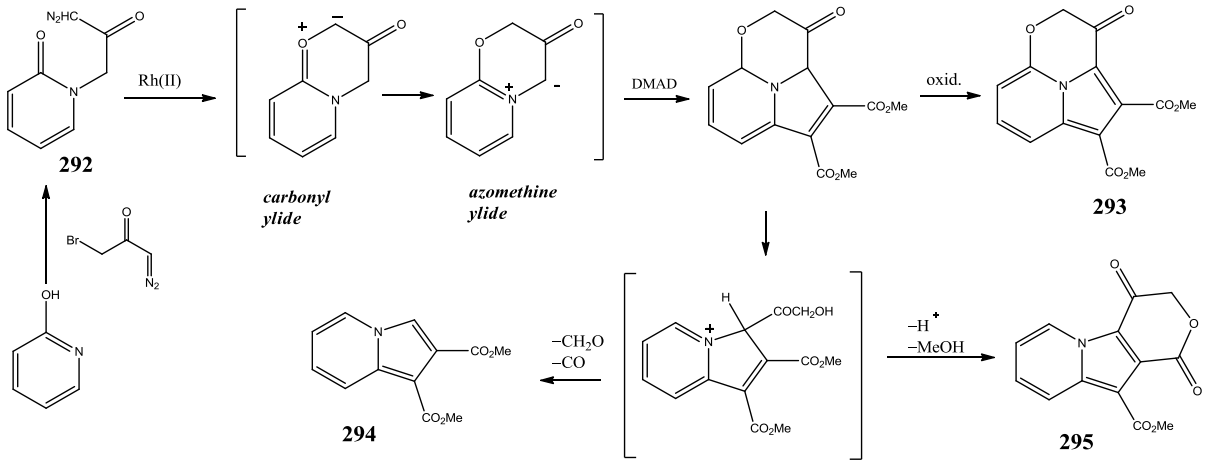
Scheme 1.99

Further investigation of tandem cyclisation/cycloaddition reactions of this compound was achieved by cycloaddition with *N*-phenylmaleimide and dimethyl fumarate (**Scheme 1.100**). Rhodium(II)-mediated cyclisation of α-diazoketone **285** in the presence of *N*-phenylmaleimide resulted in generation of the expected cycloadduct **289**. This was in contrast to the attempted cycloaddition involving dimethyl fumarate, which failed to provide an isolable sample of the cycloadduct **290**, but provided the *bis* adduct **291** upon reaction with an equivalent of DMAD.



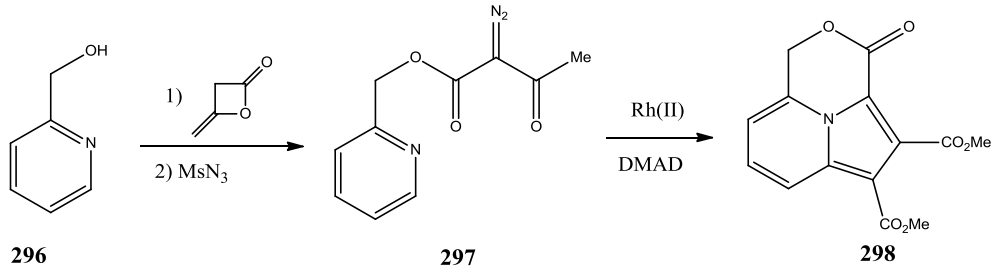
Scheme 1.100

Prompted by the success of this strategy, Padwa and co-workers subsequently prepared heterocyclic α-diazoketones derived from 2-hydroxypyridines.[253] An inherent characteristic of 2- and 4-hydroxypyridines is the existence of equilibrating hydroxyl and the pyridone tautomers, with the pyridone form generally favoured in polar solvents and the hydroxypyridine favoured in non-polar solvent systems.[254-258] This property was exploited in the synthesis of the *N*-substituted pyridone α-diazocarbonyl compound **292**, prepared in a similar manner to thio derivative **285** using an α-bromo-α'-diazoketone. Interestingly, this is the only example of a pyridone α-diazocarbonyl compound where the diazo component is tethered to the cyclic amine. Treatment of pyridone α-diazoketone **292** with rhodium(II) acetate in the presence of DMAD resulted in the formation of a variety of cycloadducts (**Scheme 1.101**). The "dipole cascade" process was also observed here with a shift from the initially formed carbonyl ylide to the more thermodynamically stable azomethine ylide. Three products were isolated from the reaction mixture, product **293** arises from aromatisation of the initially formed cycloadduct, while the pyrrole derivatives **294** and **295** result from fragmentation of the transient intermediate.



Scheme 1.101

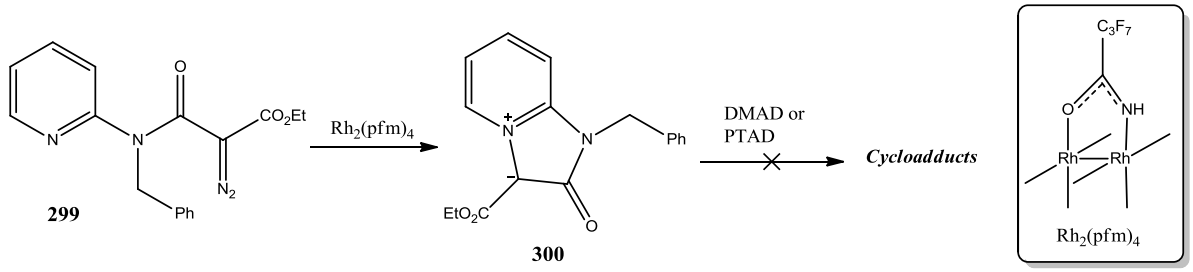
In the same work, the effect of increasing the carbon linker for the tethered α-diazocarbonyl functionality was also explored. [253] The alcohol **296** was used as substrate to prepare α-diazo-β-ketoester **297** employing acetoacetylation using diketene followed by diazo transfer. The cyclisation/cycloaddition strategy furnished the DMAD-derived cycloadduct **298** exclusively (**Scheme 1.102**).



296 **297** **298**

Scheme 1.102

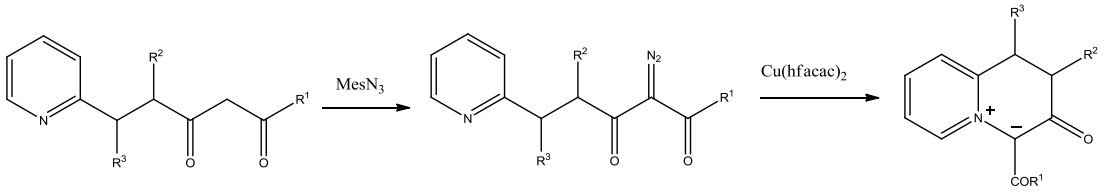
Similar pyridine-containing α-diazocarbonyl compounds were prepared by Moody to investigate competing carbenoid-mediated ylide formation *vs*. insertion processes using rhodium(II) perfluorobutyramide [$Rh_2(pfm)_4$] as catalyst (**Scheme 1.103**).[259] The pyridine diazoamide **299** presented two probable reaction pathways; either C–H insertion resulting in β-lactam formation or generation of an azomethine ylide. The ylide formation was recognised as the dominant reaction pathway with no trace of the β-lactam product. Conclusive identification of the ylide **300** was obtained by X-ray crystallography indicating this intermediate is particularly stable. Interestingly, the 6,5-membered ylide did not undergo 1,3-dipolar cycloaddition following attempted reactions with both DMAD and PTAD under a variety of conditions, in contrast to the analogous 6,6-membered azomethine ylides investigated by Padwa which readily afforded cycloadducts using the same strategy.[253]



299 **300**

Scheme 1.103

In 2001, Kostik *et al*. reported synthesis of tetrahydroquinozilinium ylides and their subsequent cycloadditions with various dipolarophiles (**Scheme 1.104**).[260] The pyridine α-diazocarbonyl compounds were synthesised from suitable 1,3-dicarbonyl compounds by diazo transfer using mesitylenesulfonyl azide ($MesN_3$). Following optimisation of conditions, the electron-deficient copper(II) bis(trifluoroacetylacetonate) was shown to be superior to the comparatively electron-rich rhodium(II) acetate catalyst for these transformations.



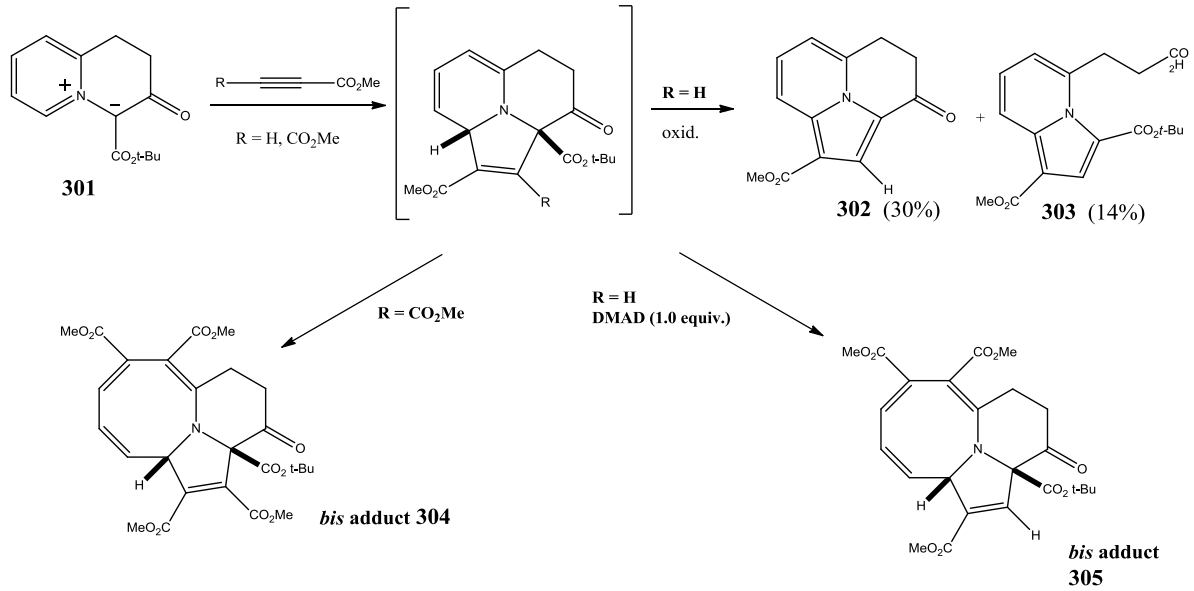
R^1 = OMe, O*t*-Bu, OBn, Me, OEt, Ph
R^2 = H, Me
R^3 = H, Me

R^1 = OMe, O*t*-Bu, OBn, Me, OEt, Ph
R^2 = H, Me
R^3 = H, Me

R^1 = OMe, O*t*-Bu, OBn, Me, OEt, Ph
R^2 = H, Me
R^3 = H, Me

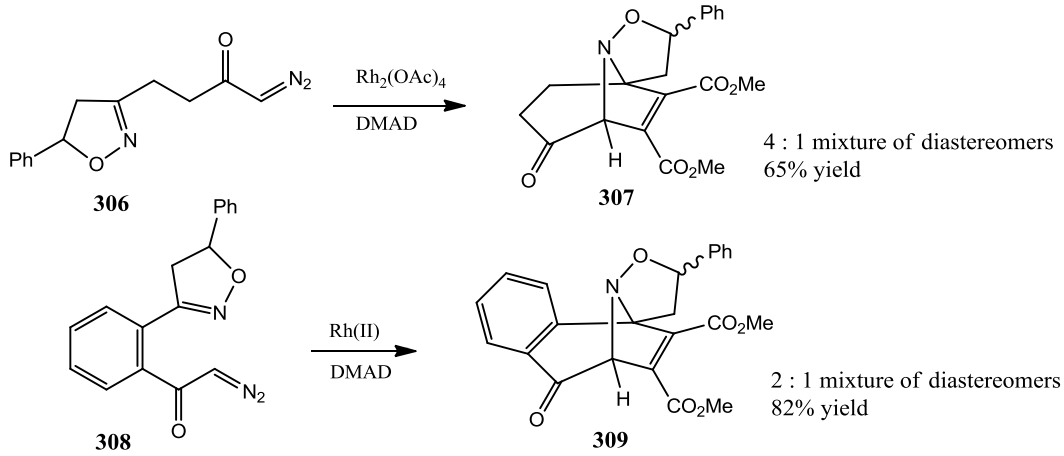
Scheme 1.104

The tetrahydroquinolizinium ylides underwent cycloaddition with methyl propiolate and DMAD forming a range of cyclazines (**Scheme 1.105**). A solvent effect was observed with cyclisations proceeding more smoothly in polar solvents such as DMSO and using an excess of dipolarophile. Reaction of azomethine ylide **301** with methyl propiolate gave the pyrrole derivative **302** as well as the ring-opened acid **303**, while reaction of the same ylide with DMAD afforded the *bis* adduct **304**. Attempted formation of a *bis* adduct using an extra equivalent (1.0 equiv.) of methyl propiolate resulted in degradation of material although addition of DMAD (1.0 equiv.) provided the desired *bis* adduct **305** in high yield.



Scheme 1.105

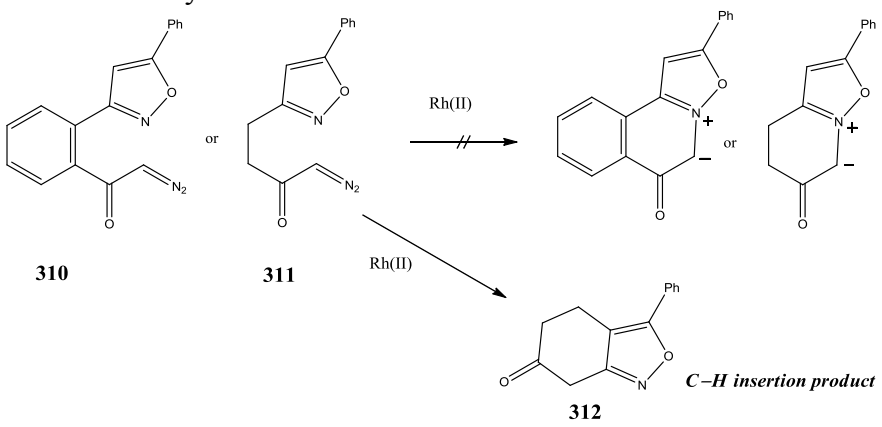
Further substrate scope was examined by Padwa using isoxazoline and isoxazole rings as substrates (**Scheme 1.106**).[261] The isoxazoline-containing α-diazoketone **306** was exposed to rhodium(II) acetate-mediated cyclisation in the presence of DMAD to afford the cycloadduct **307** as a mixture of diastereomers *via* an azomethine ylide intermediate. The related compound **308** underwent a comparable transformation with the cycloadduct **309** obtained in higher yield.



Scheme 1.106

Application of isoxazoles to provide synthetically useful 1,3-dipoles was also probed with unexpected results (**Scheme 1.107**).[261] For reactions of isoxazole α-diazocarbonyl substrates **310** and **311**, the desired azomethine ylides were not generated in either case and the recovered material from the reaction of **311** corresponded to the C–H insertion product **312**.

Padwa attributed this to the low basicity of the nitrogen on the isoxazole ring (pK_a −2.7), inhibiting formation of the ylide.[261]



Scheme 1.107

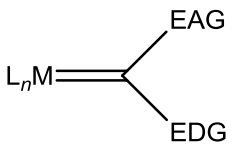
In conclusion, 1,3-dipolar cycloadditions of carbonyl, thiocarbonyl and azomethine ylides allows the formation of oxygen-, sulfur- and nitrogen-containing polycyclic systems in a rapid manner from a broad substrate pool *via* both intermolecular and intramolecular processes. Interestingly, in certain cases the reaction pathways are substrate specific with minor substitutions in the ylide or the dipolarophile resulting in different reaction outcomes.

1.5.4. Cyclopropanation

Cyclopropanation represents one of the key reactions of α-diazocarbonyl compounds as both intermolecular and intramolecular cyclopropanation processes have been extensively examined.[76,100-105,174,262,263] Intermolecular cyclopropanation is the standard method for carrying out preliminary investigations of newly-developed chiral catalysts using the standard cyclopropanation of styrene by ethyl diazoacetate. Intramolecular cyclopropanation appears to favour formation of 5,3-membered ring systems,[264] although larger ring sizes of 6,3-membered bicyclic rings,[265-267] as well as macrocyclic lactones of 9–20-membered ring sizes have also been prepared.[268-272] In addition, cyclopropanes can also provide access to intermediates for further synthetic adaptation, exemplifying this methodology as a significant synthetic platform. In this section intermolecular and intramolecular cyclopropanations are discussed, while reactions involving initial cyclopropanation and subsequent further reactions are also addressed.

1.5.4.1 Intermolecular cyclopropanation

Since the 1980's, Davies has been at forefront in the development of a specific class of transient rhodium carbenoid intermediates, donor/acceptor carbenoids (**Figure 1.9**).[273] These metallocarbenoids display an enhanced stability in comparison to traditional ones due to the ability of the donor group to temper the reactivity of the carbenoid.[85,274,275] This increased stabilisation allows the donor/acceptor systems to successfully undergo chemo- and stereoselective transformations.



EAG = Electron Accepting Group
(CO_2R, COR, $CONR_2$, CN, $PO(OR)_2$, SO_2R, NO_2, CF_3

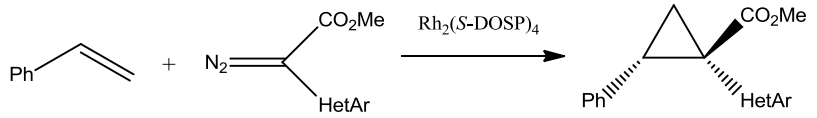
EDG = Electron Donationg Group
(vinyl, aryl, alkynyl, heteroaryl)

donor/acceptor metallocarbenoid

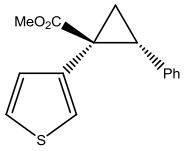
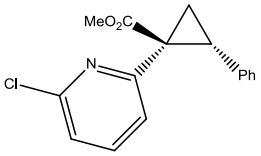
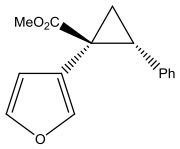
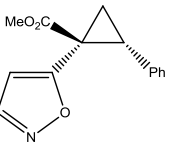
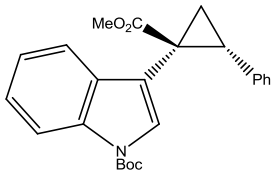
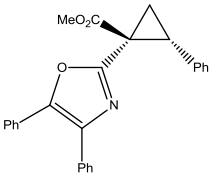
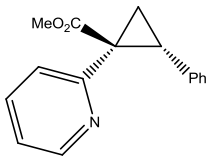
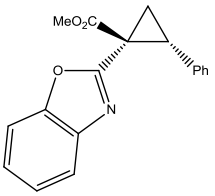
Figure 1.9: Donor/acceptor metallocarbenoids

Within this programme, Davies has employed this approach using a class of donor/acceptor carbenoids capable of highly diastereoselective intermolecular cyclopropanations, namely heteroaryldiazoacetates (**Table 1.12**).[45] The various α-diazocarbonyl compounds **313** were reacted with styrene in the presence of Rh_2(*S*-DOSP)$_4$ to provide the cyclopropane products **314**. This catalyst gave high enantioselectivites for most of the substrates investigated with the exception of *N*-Boc indolediazoacetate and methyl pyridyldiazoacetate. The results show a broad scope of substrate compatibility towards synthesis of enantioenriched cyclopropanes bearing multiple chiral centres.

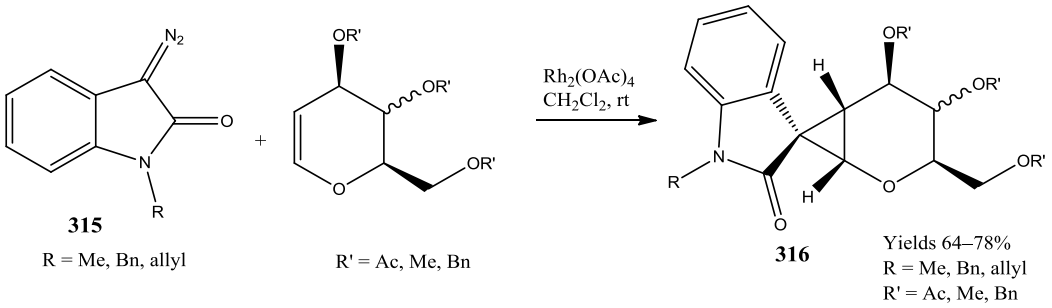
Table 1.12[276]



313 **314**

Product	Yield (%)	de (%)	ee (%)	Product	Yield (%)	de (%)	ee (%)
	87	96	89		79	98	72
	91	96	86		84	93	86
	82	94	12		81	96	71
	58	91	47		68	85	71

Very recently, Reddy and co-workers have reported highly stereoselective intermolecular cyclopropanations of glycals with cyclic α-diazoamides possessing a 1,3-dihydro-2*H*-indol-2-one skeleton.[277] Cyclopropanation of the alkene with diazoamide **315** was achieved under mild conditions employing rhodium(II) acetate as catalyst to afford a range of spirooxindole sugar derivatives **316** in high yields and excellent diastereocontrol (**Scheme 1.108**). Alternative catalysts such as CuOTf, Cu(OTf)$_2$, $PdCl_2$, Pd(OAc)$_2$ and $RhCl_3$ were explored for this transformation but failed to provide the desired spirooxindolyl sugars under the same reaction conditions.

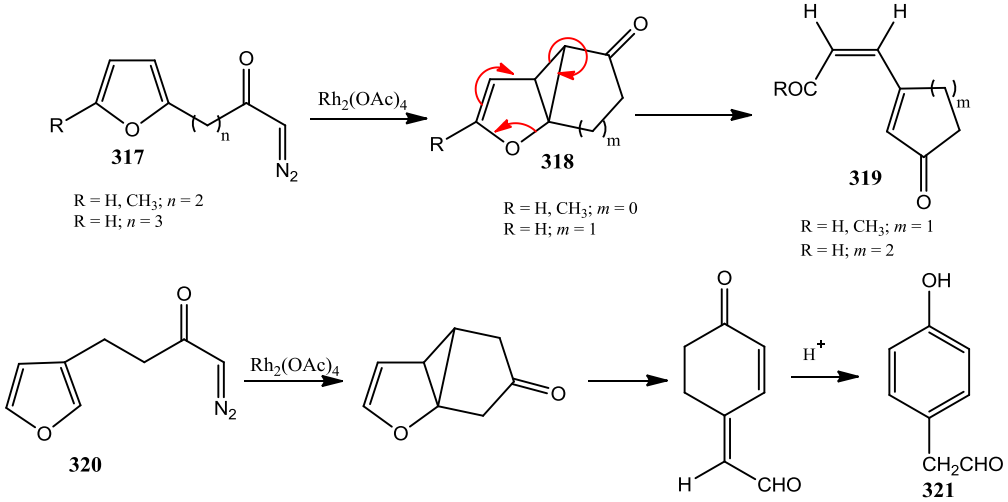


Scheme 1.108

1.5.4.2 Intramolecular cyclopropanation

Intramolecular cyclopropanation involving heterocyclic α-diazocarbonyl substrates has not received the same attention as corresponding intermolecular reactions, with debate in some cases as to whether the transformations proceed by intramolecular cyclopropanation or by means of a formal intramolecular C–H insertion.[131-133,135,136] In 1986, Padwa reported the first examples of intramolecular cyclisations of α-diazocarbonyl compounds derived from furans and benzofurans leading to a series of substituted cycloalkenones.[138] These reactions are thought to proceed *via* an initial intramolecular cyclopropanation of an α-keto carbene across the furanyl double bond to give an oxabicyclo[3.1.0]hex-2-ene intermediate, followed by an electrocyclic ring-opening reaction. The effect of the length of the side-chains on the distribution of products was investigated.

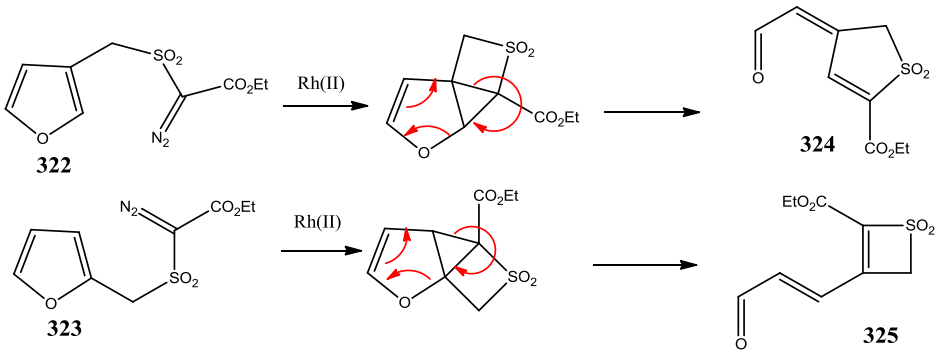
For the 2-substituted furanyl system **317**, cyclisation in the presence of rhodium(II) acetate generated a cyclopropane intermediate **318** which underwent ring scission to provide cycloalkenones **319** (**Scheme 1.109**). Reaction of the analogous 3-substituted derivative **320** resulted in formation of product **321** in high yield. This originates from initial cycloreversion of the cyclopropyl intermediate and subsequent aromatisation under acidic conditions to generate the *p*-hydroxyphenylacetaldehyde **321**. Similar examples of this methodology were demonstrated by Wenkert and co-workers on related furan substituted α-diazocarbonyl systems resulting in the formation of unsaturated ketones as the only isolable products.[278,279]



Scheme 1.109

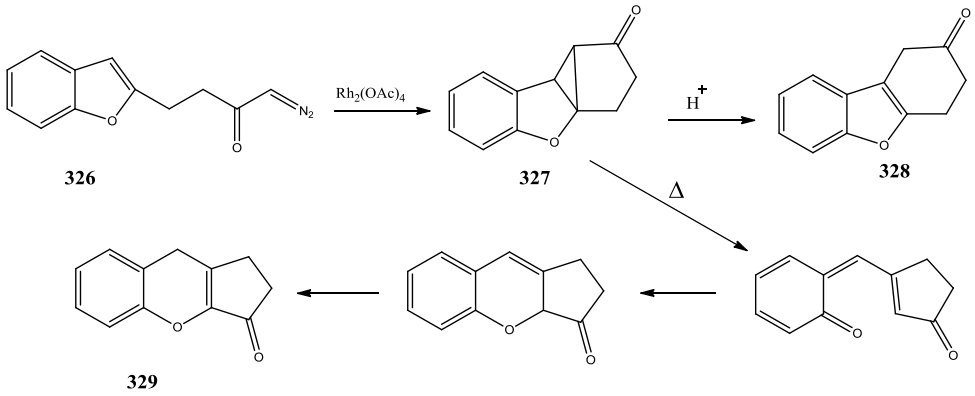
In 1989, Durst reported intramolecular insertion into aromatic C–H bonds for indole and thiophene α-diazo-β-sulfonylesters, as well as attempted C–H insertions for furan derivatives **322** and **323**.[137] In the cyclisations of the furan α-diazocarbonyl compounds, a similar

outcome was observed to the systems investigated by Padwa (**Scheme 1.110**).[138] Reaction of the rhodium carbenoid resulted in initial cyclopropanation followed by ring-opening of the intermediates to provide the unsaturated aldehydes **324** and **325** respectively, incorporating the sulfone unit as part of the rearranged ring.



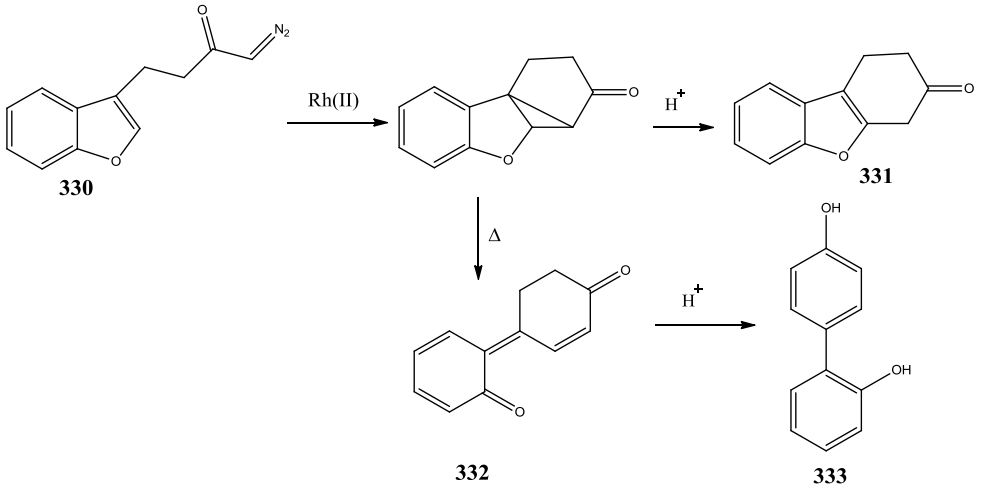
Scheme 1.110

Rhodium(II) acetate-catalysed reaction of the corresponding 2- and 3-substituted benzofuran α-diazoketones initially provided the respective cyclopropanes.[138] For the 2-substituted derivative **326** (**Scheme 1.111**), treatment of the cyclopropane **327** with acid led to ring-opening to furnish dihydrobenzofuranone **328**. However, heating of the cyclopropyl intermediate directed an alternative reaction pathway involving initial cyclopropane ring cleavage, formation of the six-membered ring and isomerisation giving the chromene-2-one derivative **329**.



Scheme 1.111

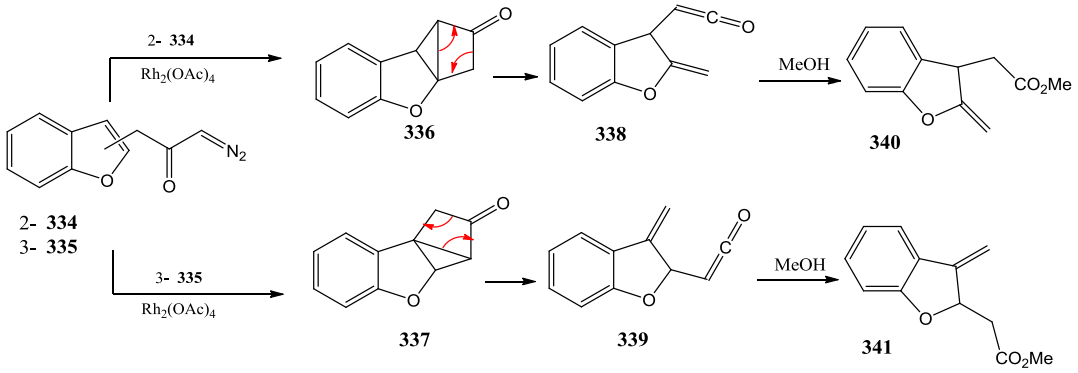
For the 3-substituted benzofuran **330** (**Scheme 1.112**), ring-opening of the resulting cyclopropane gave the corresponding tricyclic dihydrobenzofuranone **331**.[139] Further functionalisation of the cyclopropane intermediates was achieved by thermal rearrangement providing a dione **332**, which underwent a series of hydrogen shifts to furnish diphenol **333**.



330 **331** **332** **333**

Scheme 1.112

Work by Capretta on benzofuran α-diazoketones **334** and **335** posessing a shorther methylene tether gave altogether different results to the higher homologues (**Scheme 1.113**).[141] These reactions underwent expected cyclopropanation but the intermediates **336** and **337** did not fragment by [4+2]-cycloreversion, proceeding instead by a ring-opening retro [2+2]-reaction involving vinylogous Wolff rearrangement to generate the ketenes **338** and **339**. This was followed by formation of corresponding esters **340** and **341** through reaction of the ketenes with methanol. These interesting results clearly demonstrate that the extra strain arising from the shorter methylene tether alters the reactivity of the cyclopropane intermediates, leading to incongruous chemistry for these systems.

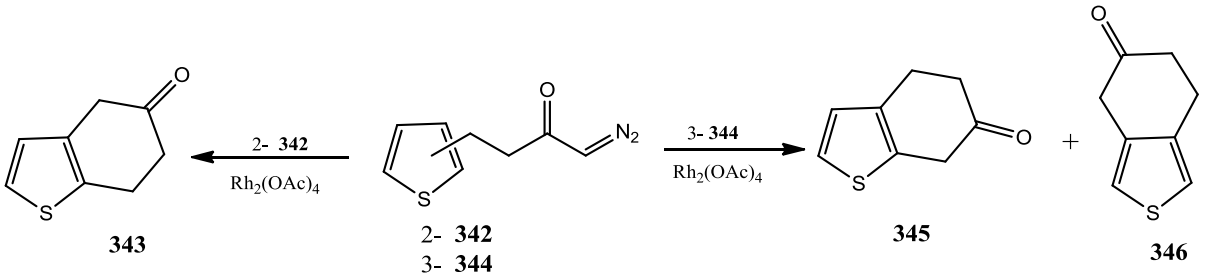


336 **338** **340**

337 **339** **341**

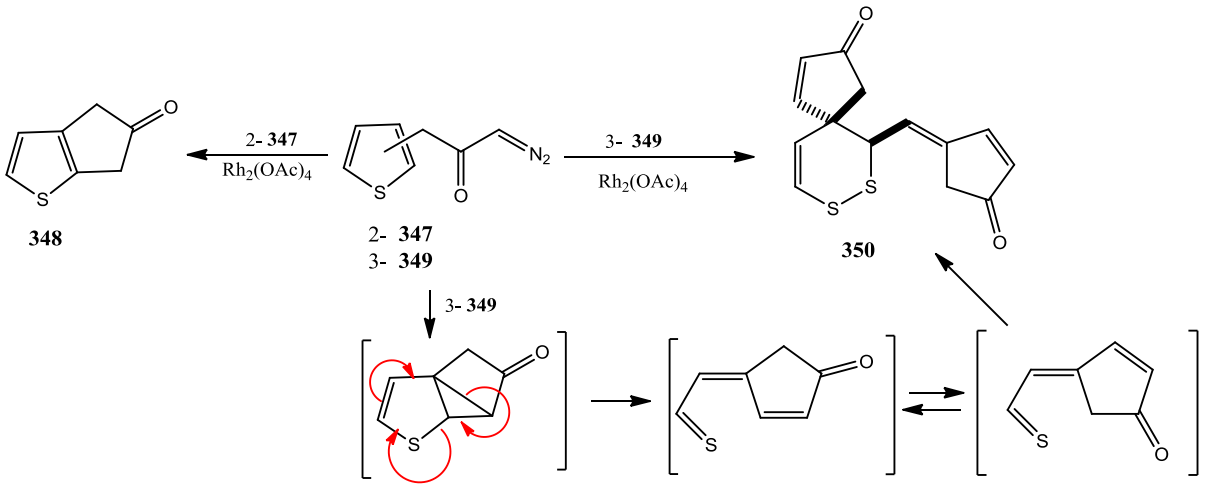
Scheme 1.113: Capretta work on shorter methylene linkers

Padwa and Capretta have extended this work to the analogous thiophene α-diazoketones to determine whether a similar mechanism is responsible for the product formation, regardless of the heteroatom on the ring (**Schemes 1.114**[139] and **1.115**[140]). Initially, Padwa inspected cyclisation of 2-substituted thienyl α-diazoketone **342** in the presence of rhodium(II) acetate, which proceeded by expected formation of a tricyclic intermediate.[139] Attempted purification by flash chromatography resulted in formation of the rearranged benzothiophen-5(4*H*)-one **343**, analogous to the benzofuran series (**Schemes 1.111** and **1.114**). Transition metal-mediated reaction of the 3-substituted thienyl α-diazoketone **344** afforded the expected rearranged product **345**, as well as a minor product **346**. The rationalisation for the mechanism is that the α-keto carbene adds across the 2,3-π-bond followed by ring-opening in the case of **345**. The minor product **346** can be considered to arise in a similar manner from initial addition across the 4,5-π-bond followed by a ring-opening reaction. The minor product could also be derived from a formal C–H insertion reaction into C(4)–H of the the thiophene ring due to the conformational flexibility of the side-chain.



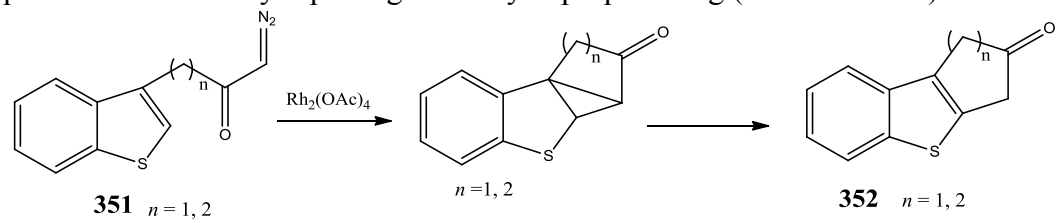
Scheme 1.114

Capretta later examined the reaction pathways of thienyl α-diazocarbonyl compounds posessing a shorter side-chain linker to investigate if the extra strain on the system results in different reaction pathways to the higher homologues (**Scheme 1.115**).[140] Rhodium(II)-catalysed transformation of 2-substituted α-diazoketone **347** afforded the expected bicyclic product **348** in 54% yield, whereas the 3-substituted derivative **349** underwent an alternate pathway only previously observed for the furanyl compounds investigated by Padwa. Initial [4+2]-cycloreversion was followed by isomerisation and Diels-Alder dimerisation to result in the formation of the spiro product **350**.



Scheme 1.115

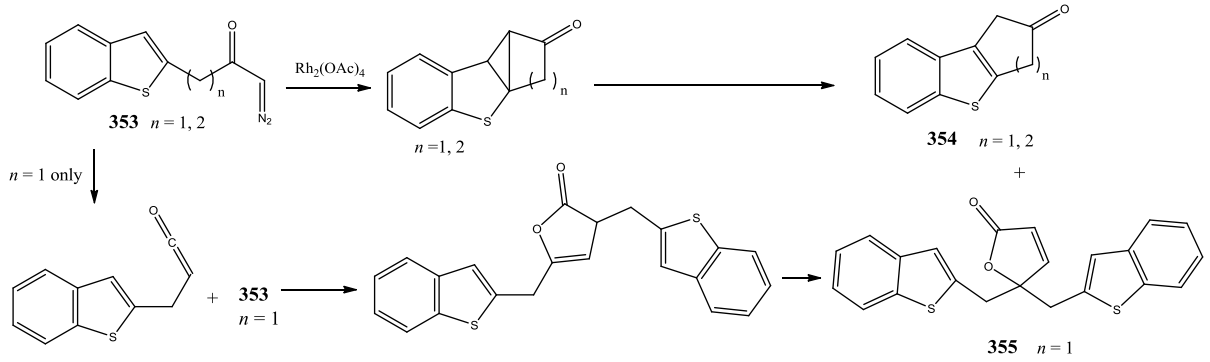
In an extension of this work, Capretta prepared benzothienyl α-diazoketones containing a short aliphatic tether to ascertain whether comparable results to the thienyl series were observed.[141] The 3-substituted derivatives **351** provided expected products **352** *via* initial cyclopropanation followed by rupturing of the cyclopropane ring (**Scheme 1.116**).



Scheme 1.116

Carbenoid-mediated reactions of the 2-substituted systems **353** afforded the expected tricyclic products **354**, as well as a dimeric product **355** when the shorter one-carbon linker was utilised (**Scheme 1.117**). Wolff rearrangement of the α-diazocarbonyl compound generated a ketene which subsequently underwent a [3+2]-cycloaddition with **353** followed by a [1,3]-alkyl shift to furnish the dimer **355**. This is an unexpected reaction pathway which can be

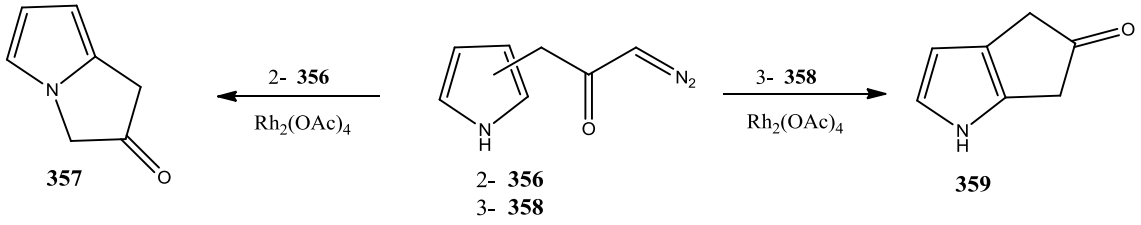
ascribed to the shorter aliphatic tether resulting in highly strained cyclobutanones, leading to atypical chemistry for the benzothiophene series.



Scheme 1.117

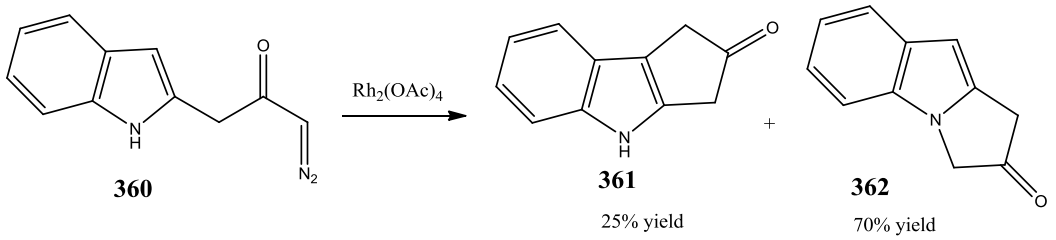
After investigating the related furanyl, benzofuranyl, thienyl and benzothienyl systems, Capretta and co-workers extended the range of α-diazocarbonyl precursors for carbenoid-mediated intramolecular cyclopropanation to include pyrrole and indole derivatives.[142] Once again, the point of attachment of the methylene linker and the size of this linker (*e.g.* two-, three- or four-atom linkers) were varied to determine the influence of this on the product distribution.

In the reactions of pyrrole substituted α-diazocarbonyl compounds (**Scheme 1.118**) the position of the side-chain determines the regiochemistry of the product. In the cyclisation of the 2-substituted pyrrole derivative **356**, the proximity of the α-diazocarbonyl moiety to the N–H bond favours formation of the N–H insertion product **357**. However, transition metal-catalysed reaction of 3-substituted α-diazoketone **358** generated the bicyclic product **359** *via* an initial cyclopropanation, followed by ring-opening or possibly by a formal intramolecular C–H insertion.

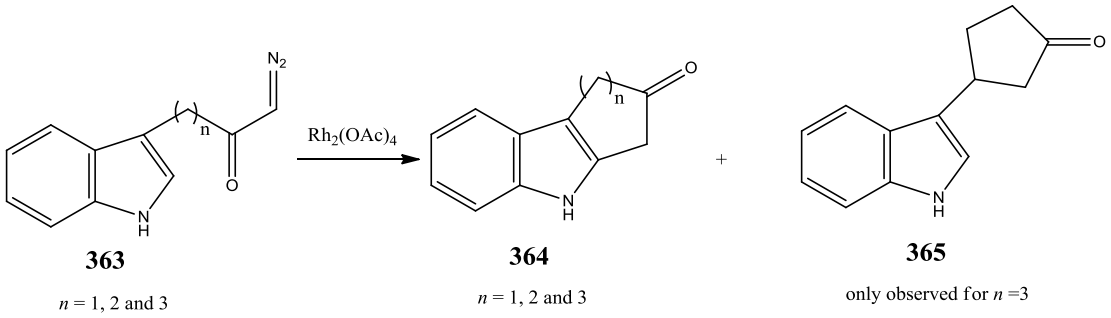


Scheme 1.118

The indole α-diazocarbonyl series exhibited similar reaction pathways as observed for the pyrrole analogues, with the isolation of both the N–H insertion and ring-opened bicyclic product. Cyclisation of 2-substituted indole α-diazoketone **360** in the presence of rhodium(II) acetate provided the ring-opened product **361** and N–H insertion product **362** (**Scheme 1.119**), analogous to the 2-substituted pyrrole derivative (**Scheme 1.118**). The 3-substituted indole α-diazoketones **363** afford the corresponding tricyclic compounds **364** in all cases, as well as a C–H insertion product **365**, observed for the higher homologue (n = 3) (**Scheme 1.120**).

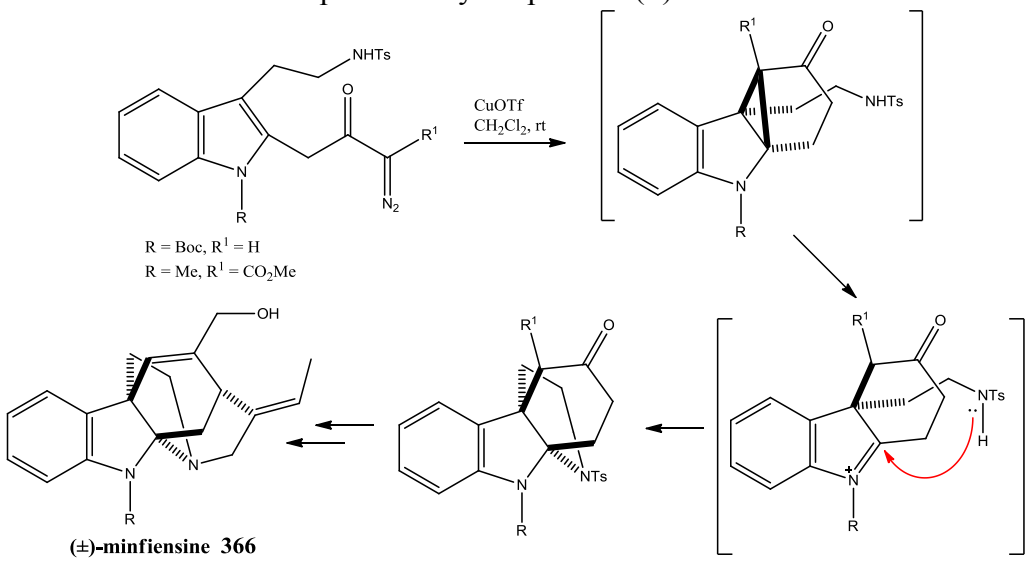


Scheme 1.119



Scheme 1.120

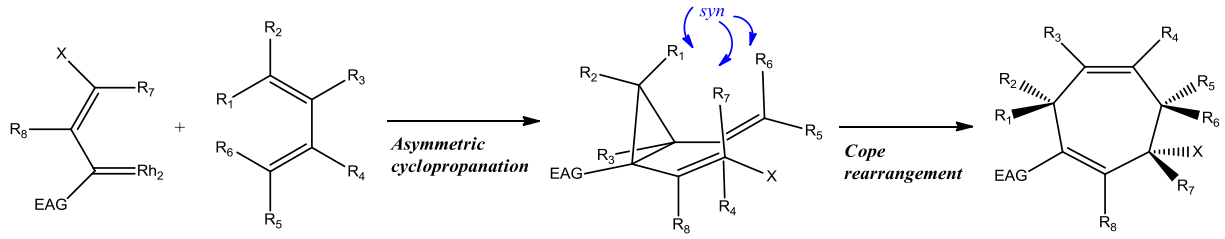
Qin has generated the tetracyclic core of natural product (±)-minfiensine **366** by application of the intramolecular cyclopropanation methodology (**Scheme 1.121**).[280] This advanced intermediate was further elaborated into the desired pentacyclic alkaloid **366** using a convergent 12-step route in an overall yield of 4%. Critically, the tosyl-protected amine serves to intercept the indolenium cation to construct the fourth ring, while the keto (or enol) functionality is advantageous in the generation of the final ring of the pentacycle. Qin has further demonstrated the application of intramolecular cyclopropanation using an indole-substituted α-diazo-β-ketoester in establishing the highly functionalised precursor, which was later modified to afford the complex hexacyclic product (±)-communesin F.[281]



Scheme 1.121

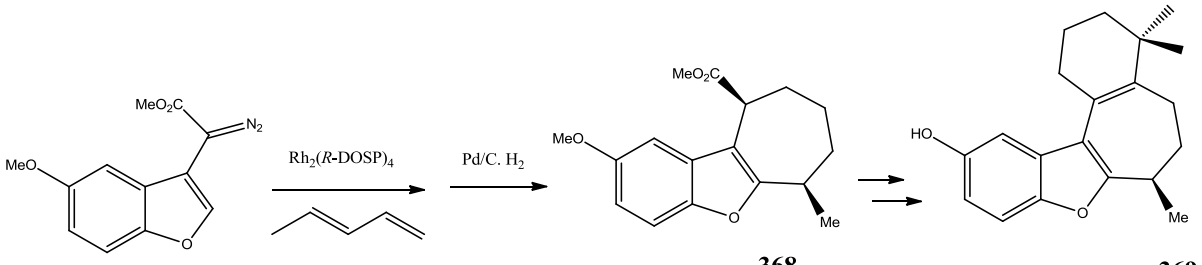
1.5.4.3 [4+3]-Cycloaddition of vinyl carbenoids

Another example of Davies' donor/acceptor carbenoid systems are vinyldiazoacetates which can react with dienes in an intramolecular [4+3]-cycloaddition *via* an initial cyclopropanation, followed by a Cope rearrangement of the newly-formed divinylcyclopropane. This methodology allows the formation of cycloheptadienes possessing three stereocentres in a single synthetic step, allowing excellent diastereo- and enantiocontrol.[282] Davies has suggested the Cope rearrangement of the *cis*-divinylcyclopropanes proceeds through a boat-like transition state to afford the seven-membered products.[274] A generalised example is shown below (**Scheme 1.122**).



Scheme 1.122: General example of Cope rearrangement[276]

Heteroaryldiazoacetates have proven useful substrates in the assembly of the 6,5,7-fused framework of (+)-frondosin B (**Scheme 1.123**).[283] The benzofuran α-diazoacetate **367** was reacted with *trans*-piperylene in the presence of Rh_2(*R*-DOSP)$_4$ catalyst, followed by hydrogenation with palladium on carbon to furnish the reduced [4+3]-cycloadduct **368**. This tricyclic product **368** is an advanced intermediate previously converted to (+)-frondosin B **369** by Danishefsky and co-workers through a short synthetic sequence.[284]



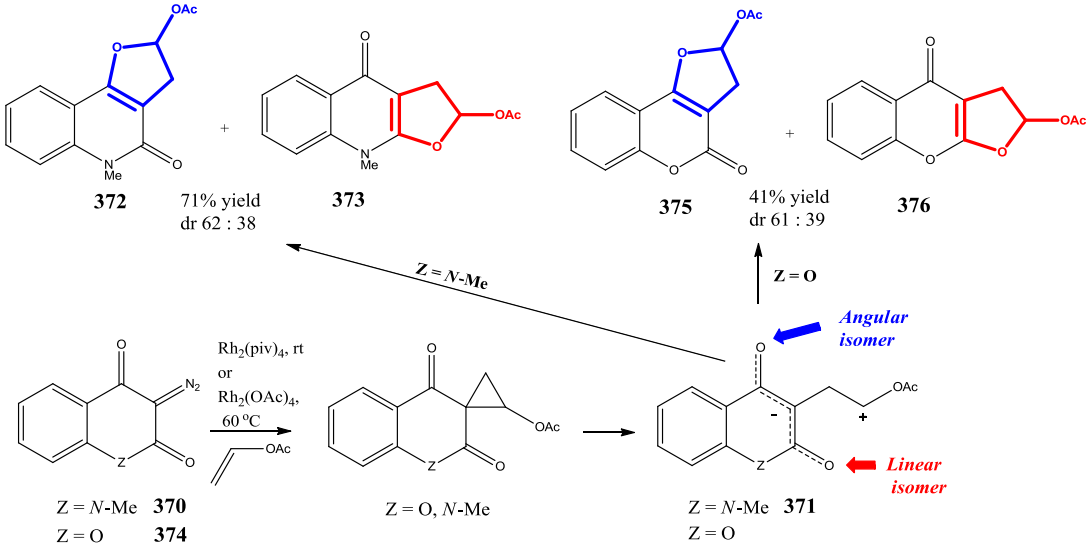
Scheme 1.123

1.5.4.4 Cyclopropanation followed by 1,3-dipolar ketocarbene addition

In 1999, Pirrung investigated the intermolecular dipolar cycloaddition of a series of α-diazoquinolinediones with alkenes or alkynes such as vinyl acetate and trimethylsilylacetylene (**Scheme 1.124**).[285] A key property of these α-diazocarbonyl systems is the presence of two carbonyl functionalities in the compound. Cyclisation of *N*-methyl diazoquinolinedione (X = *N*-Me) **370** in the presence of rhodium(II) acetate results in initial cyclopropanation and subsequent ring-opening. Following unravelling of the cyclopropane ring, the two carbonyl moieties exhibit a balanced distribution of electron density over a five-atom chain **371**. These sites serve as the regions of highest electron density, thereby favouring cycloaddition, resulting in generation of both regioisomers **372** and **373** in the reactions of **370** with vinyl acetate and trimethylsilylacetylene. It was observed that substitution of the N–H bond was critical for the cycloaddition to occur. At a later stage in this investigation, it was identified that addition of a few drops of hydrochloric acid ethanolate to the reaction

mixture resulted in significantly favoured formation of what Pirrung has termed the angular isomer over the linear isomer.

In the same year, Lee and co-workers examined carbenoid-mediated reactions of related 3-diazo-2,4-chromenediones **374** (X = O) in pursuit of generating the skeletal framework of naturally occurring coumarins and dihydrofurocoumarins.[286] Reaction of **374** with vinyl acetate in the presence of rhodium(II) acetate resulted in the formation of both the angular **375** and linear **376** isomers (**Scheme 1.124**). In addition, dione **374** was reacted with nitriles, isocyanates and other ketones generating the appropriate five-membered rings with the formation of the angular isomer predominating.



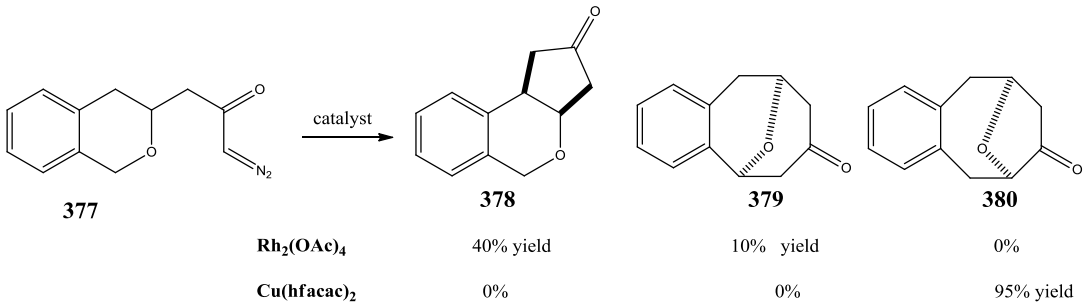
Scheme 1.124

1.5.5 Chemoselectivity in heterocyclic α-diazocarbonyl reactions

Since α-diazocarbonyl compounds can undergo a wide array of transformations, it is imperative that there is efficient control of chemoselectivity in order to synthesise specific compounds of interest. Factors controlling chemoselectivity arise from the structure of the α-diazocarbonyl substrate, as well as the electronic or steric nature of the catalyst complexes, leading to a variation in the reaction outcome. Examples of catalyst-dependent and substituent-dependent chemoselectivity involving heterocyclic α-diazocarbonyl compounds will be discussed in this section.

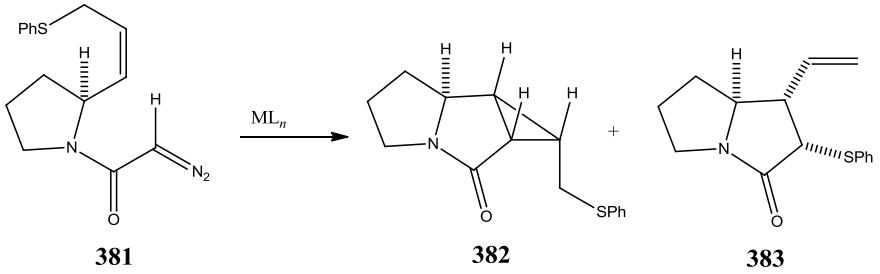
1.5.5.1 Catalyst-based chemoselectivity

Catalyst-dependent selectivity has been typified by West *et al*. in the cyclisation of α-diazoketone **377** (**Scheme 1.125**).[181] Reaction of **377** with rhodium(II) acetate resulted in the formation of both C–H insertion products **378** and **379**, whereas reaction with $Cu(hfacac)_2$ afforded the oxonium ylide/[1,2]-shift product **380** exclusively.



Scheme 1.125

During an investigation by McMills and co-workers,[287] it was ascertained that catalyst and solvent, as well as the nature of α-diazocarbonyl substrate can be significant in determining potential reaction pathways (**Scheme 1.126**). Cyclisation of *cis*-α-diazoketone **381** with different catalysts in toluene gave both cyclopropane **382** and ylide formation/[2,3]-rearrangement product **383** (**Table 1.13**). The cyclopropanation process tended to dominate in most cases. However, treatment of α-diazoamide **381** with $Rh_2(cap)_4$ in fluorobenzene displayed a dramatic switch of the product ratio with the ylide-mediated pathway now favoured (**Table 1.13**, entry 4).

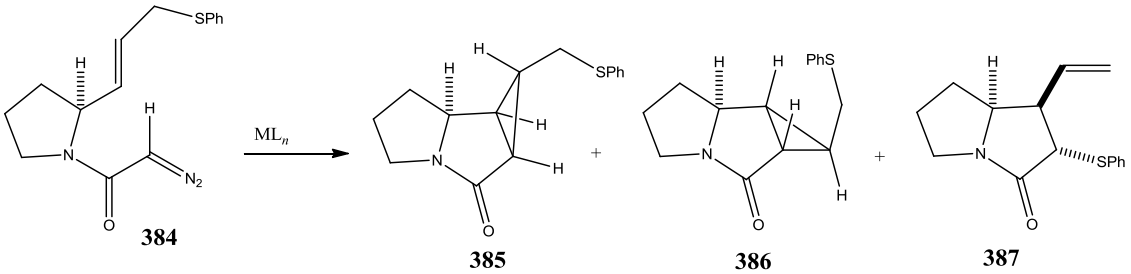


Scheme 1.126

Table 1.13

Entry	Catalyst	Solvent	Yield (%)	382 : 383
1	$Rh_2(OAc)_4$	PhH	62	66 : 34
2	$Cu(hfacac)_2$	PhH	61	92 : 8
3	$Pd(OAc)_2$	PhH	63	98 : 2
4	$Rh_2(cap)_4$	PhF	60	6 : 94

Transition metal-mediated reactions of corresponding *trans*-α-diazoketone **384** followed a similar trend (**Scheme 1.127**), resulting in predominant formation of cyclopropanes **385** and **386** upon reaction with $Rh_2(OAc)_4$, $Cu(hfacac)_2$ and $Pd(OAc)_2$ in toluene (**Table 1.14**).[287] Cyclisation of **384** in the presence of $Rh_2(cap)_4$ once again resulted in a switch in the reaction pathway, favouring the generation of tandem ylide formation/[2,3]-sigmatropic rearrangement product **387** as the major component (**Table 1.14**, entry 4).

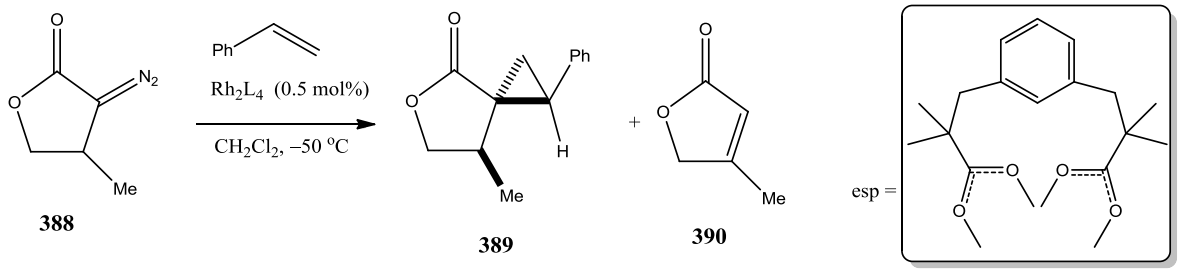


Scheme 1.127

Table 1.14

Entry	Catalyst	Solvent	Yield (%)	385 : 386 : 387
1	$Rh_2(OAc)_4$	PhH	70	34 : 31 : 0
2	$Cu(hfacac)_2$	PhH	68	68 : 32 : 0
3	$Pd(OAc)_2$	PhH	78	73 : 27 : 0
4	$Rh_2(cap)_4$	PhH	71	0 : 10 : 90

Recently, Fox and co-workers demonstrated catalyst-dependency in intermolecular cyclopropanations involving cyclic α-diazo dihydrofuran-2-ones **388** and pyrrolidin-2-ones (**Scheme 1.128**).[288] A key trend was identified during the initial study with cyclopropanation to give **389** in strong competition with an alternative β-hydride migration pathway leading to **390**. Following a lengthy catalyst screening process, the competing 1,2-hydride shift pathway could be suppressed under the optimised conditions (**Table 1.15**). When rhodium(II) trifluoroacetate was used as catalyst, the β-hydride pathway predominated, whereas in the reaction involving rhodium(II) pivalate, formation of the cyclopropane **389** was highly favoured (**Table 1.15**, entry 4 *vs.* 2).



Scheme 1.128

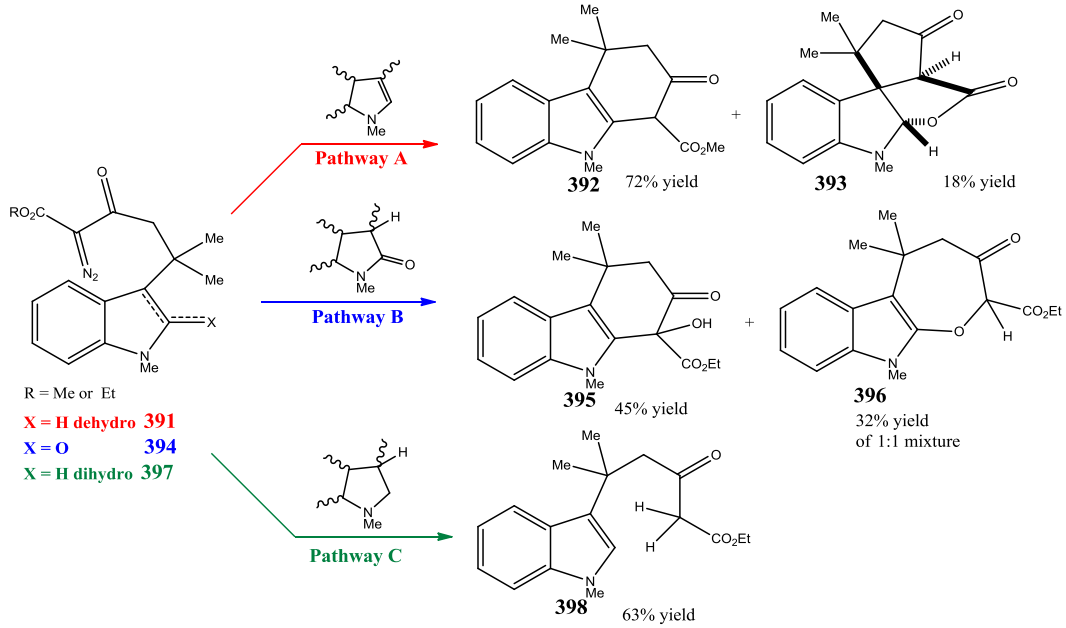
Table 1.15

Entry	Catalyst	Yield 389 (%) (dr)[a]	Yield of 390 (%)
1	$Rh_2(oct)_4$	30 (93 : 7)	38
2	$Rh_2(tfa)_4$	0	78
3	$Rh_2(esp)_2$	78 (94 : 6)	11
4	$Rh_2(OPiv)_4$	85 (95 : 5)	9

[a] Yields and diastereomeric ratio were determined by crude ^{1}H NMR analysis using mesitylene as an internal standard.

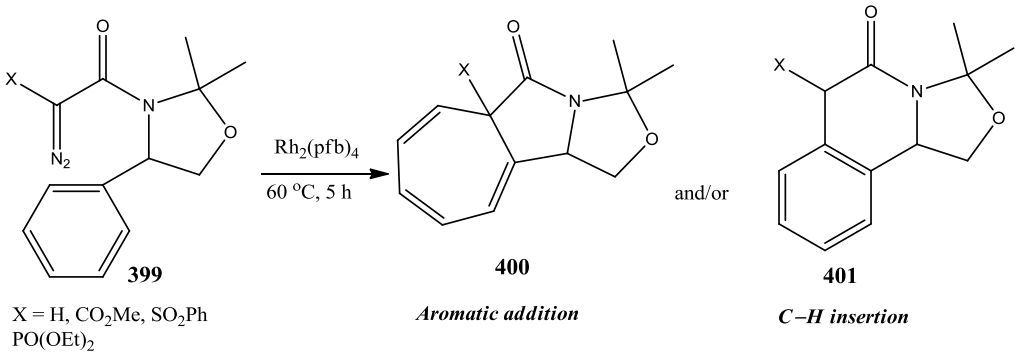
1.5.5.2 Chemoselectivity due to substituent effects

In 2001, Jung and Slowinski reported three different transition metal-mediated reaction pathways of indole-substituted α-diazo-β-ketoesters through variation of the oxidation state of the parent indole moiety (**Scheme 1.129**).[289] Treatment of **391** with rhodium(II) acetate gave rise to pathway A, furnishing the anticipated product **392** from tandem cyclopropanation and ring scission, as well as an unexpected tetracyclic spiro-derivative **393** from the same cyclopropane intermediate. For pathway B, cyclisation of α-diazo-β-ketoester **394** containing a carbonyl functional group in the presence of $Rh_2(OAc)_4$ provided two products. The isolated products included an α-hydroxy-β-ketoester **395** *via* ring-opening of a spiro-epoxide intermediate and a keto/enol seven-membered indolooxepine ring **396**, both derived from a common carbonyl ylide intermediate. Finally, in the case of pathway C, rhodium(II) acetate-mediated cyclisation of dihydroindole α-diazo-β-ketoester **397** furnished an intramolecular hydride transfer compound **398**, the formation of which is presumably driven by the aromatisation of the dihydroindole component.



Scheme 1.129

K.W. Jung has shown that different reaction pathways can be selectively controlled through an α-substituent effect in the rhodium(II)-catalysed transformations of a series of oxazolidinones **399** (**Scheme 1.130**).[290] The presence of weakly electron-withdrawing substituents in the α-position favoured formation of **400** arising from an intramolecular Buchner reaction as the major component, as well as generation of **401**, the product of formal C–H insertion pathway in low yield (**Table 1.16**). However, on switching towards strongly electron-withdrawing substituents in the α-position to the diazo moiety, the C–H insertion process was observed as the exclusive reaction outcome to furnish **401**, with no indication of formation of the aromatic addition product **400** (**Table 1.16**, entry 4 *vs.* 1).



Scheme 1.130

Table 1.16

Entry	X	400 (%)[a]	401 (%)[a]
1	H	85	–
2	COMe	65	12
3	CO_2Me	66	15
4	SO_2Ph	–	93
5	$PO(OEt)_2$	–	86

[a] Isolated yield after column chromatography.

Wee and co-workers have recently explored conformational, steric and electronic effects on the chemoselectivity for reactions of a series of *N*-(2-indolyl)-methyl α-diazoamides.[291] Some of the chemistry here overlaps with the earlier discussion on intramolecular cyclopropanation (**Section 1.5.4.3**). The structural design of the α-diazoamide substrates and potential reaction sites is illustrated below (**Figure 1.10**).

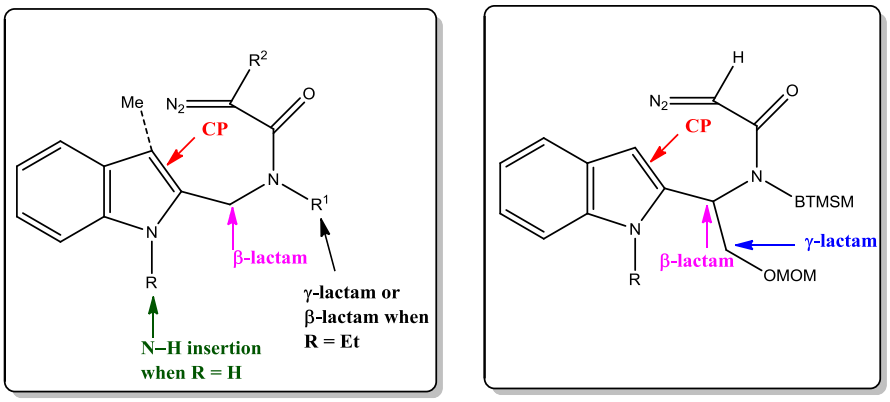


Figure 1.10: Type (i) and (ii) substrates used in α-diazocarbonyl cyclisations (diagram adapted from Wee)[291]

Initial investigations focused on substituted α-diazoamides of substrate type (i), where the R, R^1 and R^2 groups are varied. Cyclisation of **402** in the presence of rhodium(II) acetate presented several reaction pathways resulting in generation of cyclopropane, ring-opened cyclopropane product, γ-lactam, β-lactam and N–H insertion, depending on the substituents used. Replacement of the *N*-ethyl unit with the *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) protecting group at position R^1 efficiently eliminated the reaction pathway leading to γ-lactam

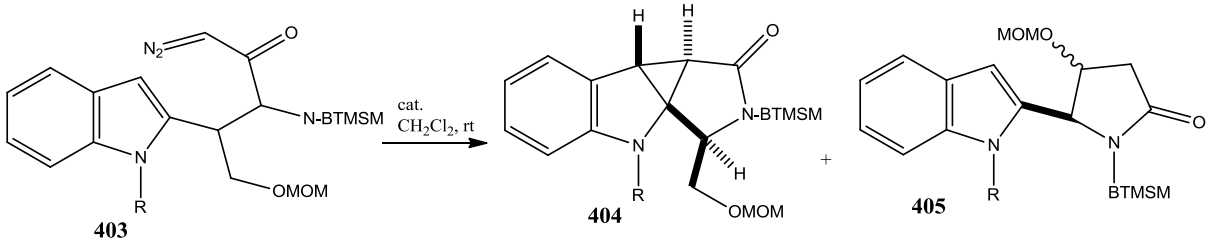
formation (**Table 1.17**, entry 1 *vs.* 4). The *N*-BTMSM also exerts conformational control resulting in metallocarbenoid C–H insertion into the available indolylmethylene, generating the β-lactam in minor to appreciable yields. These results are summarised below (**Table 1.17**).

Table 1.17: *Transition metal-catalysed cyclisations of substituted indolyl α-diazoamides, type (i)* **402**

					Relative Yield (%)[a]				
Entry	**R**	**R^1**	**R^2**	**C(3)-Me**	**CP**	**γ-lactam**	**β-lactam**	**Ring -open**	**N-H**
1	SO_2Ph	Et	CO_2Me	–	28	31	14	[b]	–
2	H	BTMSM	CO_2Me	–	–	–	17	65	8
3	Me	BTMSM	CO_2Et	–	–	–	–	100	–
4	SO_2Ph	BTMSM	CO_2Et	–	100	–	–	–	–
5	Me	BTMSM	Ac	–	–	–	50	50	–
6	SO_2Ph	BTMSM	Ac	–	100	–	–	–	–
7	SO_2Ph	BTMSM	H	–	100	–	–	–	–
8	Me	BTMSM	H	Yes	75	–	25	–	–

[a] Relative yield was calculated based on the weight ratio of the isolated products.
[b] Ring-opened product obtained after cyclopropane was left to stand at room temperature for 24 h.

After demonstrating that effective conformational control can be achieved through use of the *N*-BTMSM group, Wee *et al*. then carried out related reactions on type (ii) substrates **403**, (**Scheme 1.131**) which potentially has three sites where the metallocarbenoid can react [**Figure 1.9, type (ii)**].[291] On carrying out the transformations of α-diazoketone **403** in the presence of several rhodium(II) catalysts and copper(II) bis(hexafluoroacetylacetonate), formation of the cyclopropane **404** and the γ-lactam **405** was observed, with complete 'switching off' of the β-lactam reaction pathway. In each case, cyclopropanation was the dominant reaction outcome, while formation of the γ-lactam was observed as a significant reaction pathway employing the electron-deficient $Cu(hfacac)_2$ and $Rh_2(tfa)_4$ catalysts. In contrast, γ-lactam formation was poorly competitive using the comparatively electron-rich $Rh_2(OAc)_4$ and $Rh_2(cap)_4$ complexes.



R = SO_2Me, MOM

	404: 405	
R = SO_2Me, $Rh_2(OAc)_4$	82 : 18	98% yield
R = SO_2Me, $Rh_2(cap)_4$	91 : 9	91% yield
R = SO_2Me, $Rh_2(tfa)_4$	57 : 43	69% yield
R = SO_2Me, $Cu(hfacac)_2$	59 : 41	85% yield
R = MOM, $Rh_2(OAc)_4$	100 : 0	80% yield
R = MOM, $Rh_2(cap)_4$	100 : 0	93% yield

Scheme 1.131: Cyclisations of type (ii) diazoamides

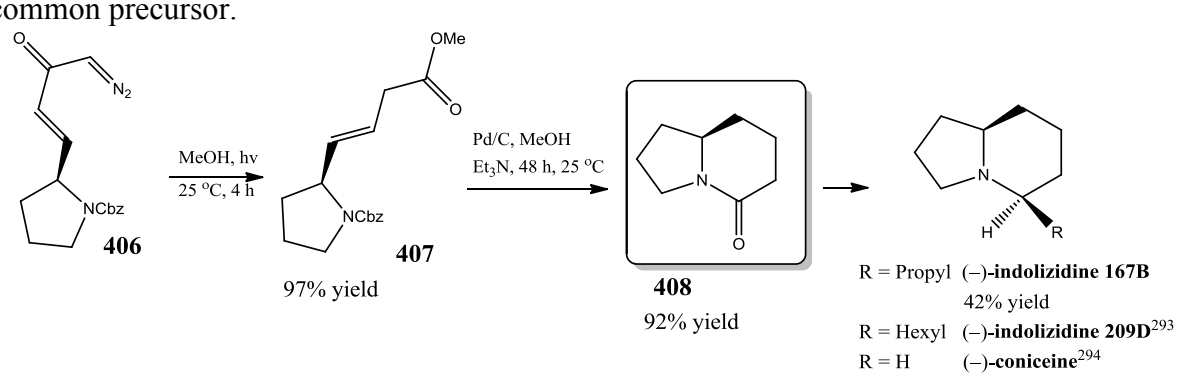
1.5.6 Miscellaneous reactions of heterocyclic α-diazocarbonyl compounds

In addition to transformations of heterocyclic α-diazocarbonyl substrates previously discussed, there are a number of additional reaction pathways and some of these are addressed here. These include the Wolff rearrangement, oxidation followed by formation of quinoxalines and 1,2-hydride shift/β-hydride migration.

1.5.6.1 Wolff rearrangement

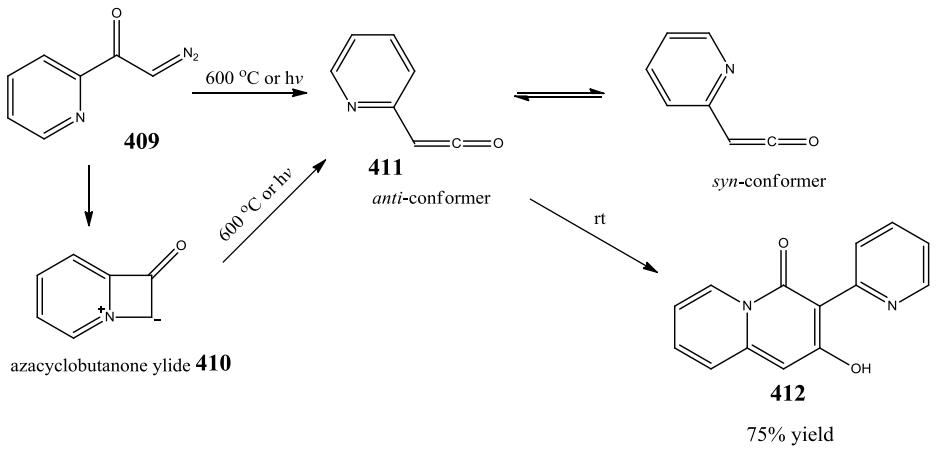
Extrusion of nitrogen from α-diazocarbonyl compounds followed by 1,2-rearrangement can generate a transient ketene, which may undergo nucleophilic attack by water, alcohols and amines. Additional possible transformations of the ketene include cycloaddition with unsaturated systems or ring-contraction in the cases of ketenes arising from cyclic α-diazoketones. Probably the best known Wolff rearrangement reaction is the Arndt-Eistert homologation of carboxylic acids.

The most conventional method to prepare carboxylic acids *via* Wolff rearrangement involves a silver salt to induce ketene formation, although it is also possible to generate the reactive ketene species by photochemical means. Recently, Burtoloso has reported an unusual photochemical Arndt-Eistert homologation using an α,β-unsaturated α-diazoketone **406** and methanol as nucleophile (**Scheme 1.132**).[292] The α,β-unsaturated ester **407** was formed in high yield and subsequent removal of the carboxybenzyl (Cbz) protecting group in the presence of triethylamine results in concomitant double bond reduction and cyclisation to generate lactam **408**. This lactam **408** is a useful synthetic precursor which was converted to (–)-indolizidine 167B in 42% yield. In addition, this compound allows ready access to related alkaloids with (–)-indolizidine 209D[293] and (–)-coniceine[294] previously synthesised from this common precursor.



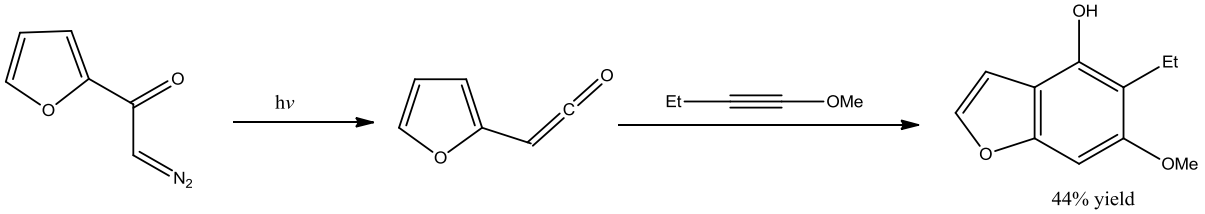
Scheme 1.132

Pyridylketenes, which are prepared by vacuum pyrolysis of the corresponding α-diazoketones have been investigated by Wentrup[295] and Tidwell (**Scheme 1.133**).[296-298] The ketene conformers are trapped in a matrix and identified by infrared stretching frequencies differentiating between the *syn*- and *anti*-conformers. Another product was observed in the case of the 2-diazo-1-(pyridin-2-yl)ethanone **409**, with generation of an azacyclobutanone ylide **410**, identified by infrared spectroscopy. The azomethine ylide rearranges to the *anti*-conformer **411** upon further photolysis or high temperatures. This *anti*-conformer can also undergo a cyclodimerisation pathway at room temperature to furnish **412**.[295] The 2-, 3-, and 4-pyridyl ketenes were prepared by this method and in the case of the 4-pyridyl ketene, introduction of water or amine provided the acetic acid or amide derivative.[297]



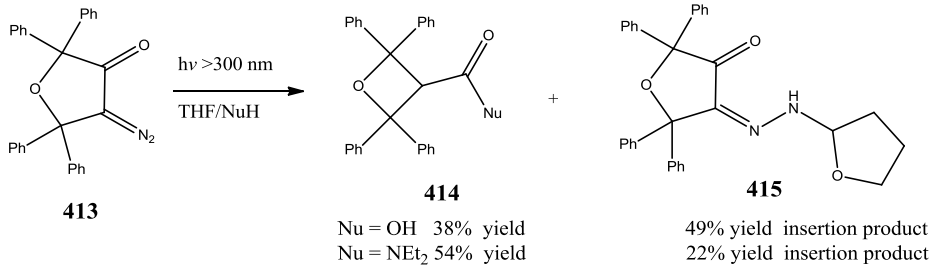
Scheme 1.133

Other heteroarylketenes, such as furan, thiophene, *N*-Boc pyrrole and *N*-Boc indole were prepared from their α-diazoketone analogues by Wolff rearrangement. These reactive intermediates underwent a domino process involving three pericyclic reactions; namely [2+2]-cycloadditions with alkynes, 4π electrocyclic ring-cleavage and a 6π electrocyclic ring-closure to afford a series of polycyclic heteroarenes (**Scheme 1.134**).[299]



Scheme 1.134

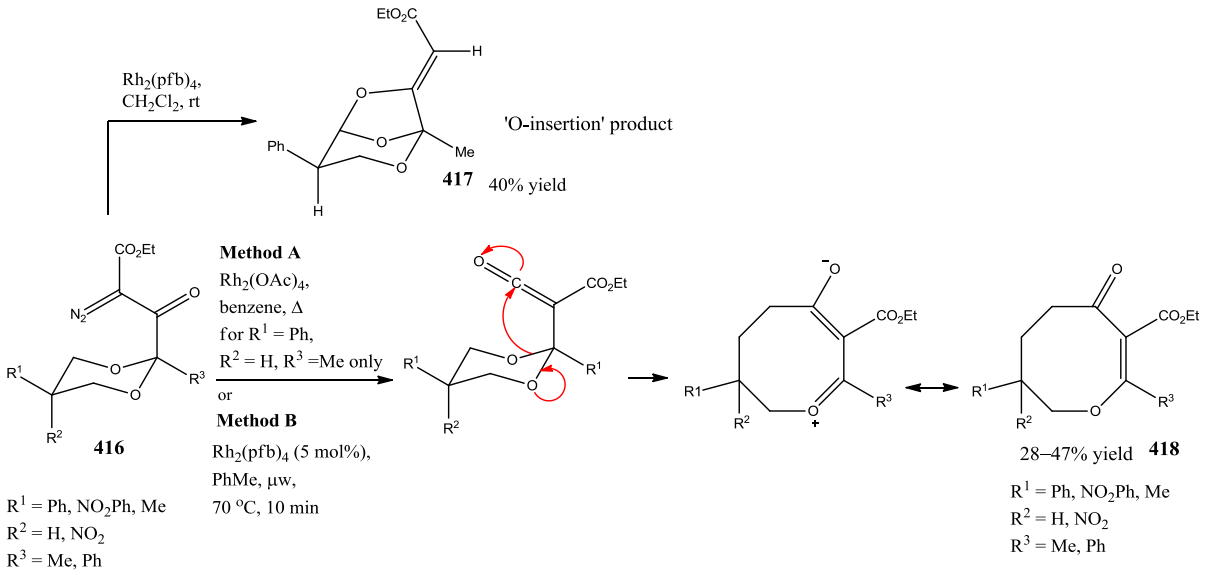
Nikolaev has observed some intriguing results while investigating photochemical reactions of tetraphenyl-substituted α-diazotetrahydrofuranone **413** (**Scheme 1.135**).[300] Following photolytic reaction of the tetrahydrofuran-containing diazo substrate **413** in a solution of THF/nucleophile, the expected ring-contraction product **414** was generated as well as identification of an unanticipated adduct **415** as the major component. This adduct originates from insertion of the terminal nitrogen atom of the diazo group into the α-C–H bond of tetrahydrofuran.



Scheme 1.135

In 2009, Steel reported a novel skeletal rearrangement of acetal-containing α-diazoketones giving medium-sized ring lactones by way of the Wolff rearrangement (**Scheme 1.136**).[301] Reaction of the acetal α-diazoketone **416** in the presence of $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ afforded two distinct products whose formation was found to be temperature-dependent, an 'O–insertion' product **417** and the ring-expanded product **418**. When the reaction was conducted at room temperature using dichloromethane as solvent, formation of the bicyclic

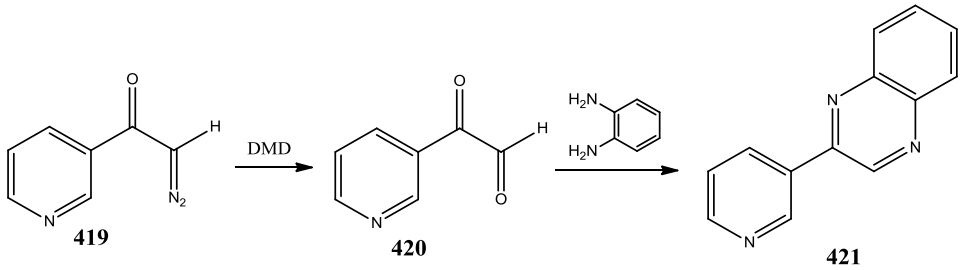
product **417** was favoured, while use of higher temperature in benzene or toluene predominantly favoured generation of the 8-membered lactone **418** by both thermal and microwave irradiation in low to moderate yield. Interestingly, generation of the 'O-insertion' product **417** would appear to originate through a similar mechanism, *i.e.* oxygen-assisted hydride transfer, as previously observed in this review for similar substrates investigated by Wardrop and Forslund (**Scheme 1.30**).[129] Steel has postulated that use of higher temperatures may induce dissociation of the metallocarbenoid to furnish the free carbene, giving rise to the Wolff rearrangement pathway.



Scheme 1.136

1.5.6.2 Oxidation of α-diazocarbonyl compounds and condensation with diamines

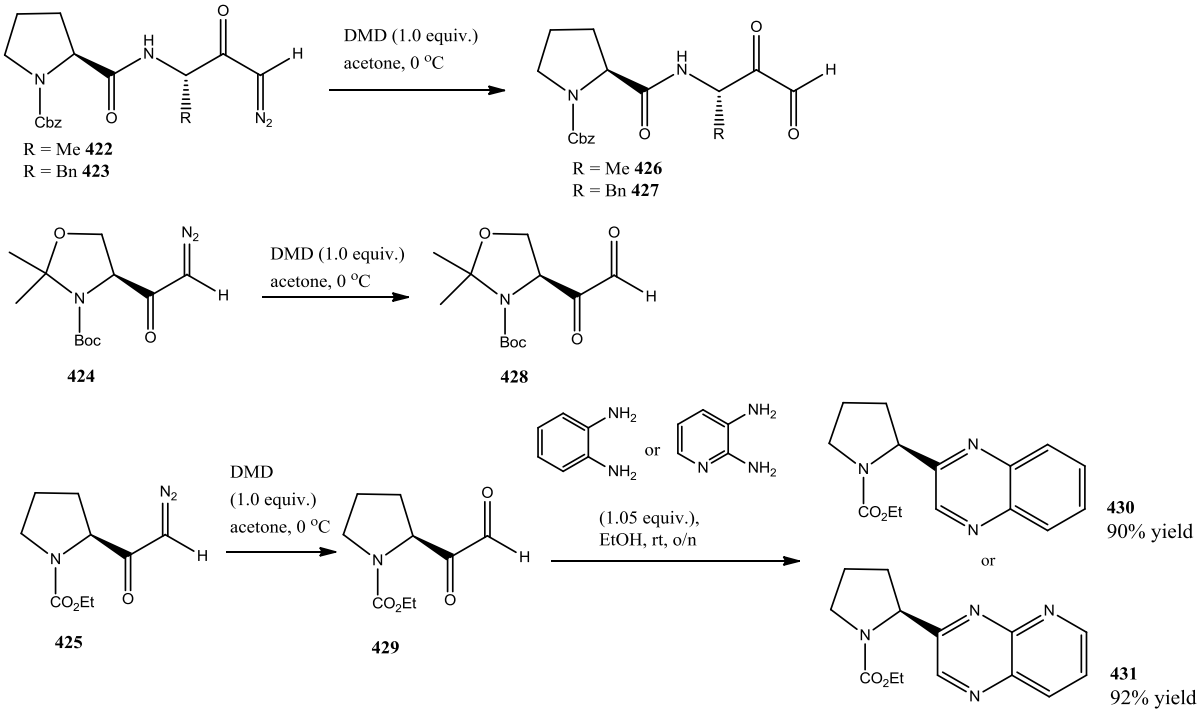
Oxidation of a diazo group can be implemented to introduce further carbonyl functionality to a compound and is useful for the preparation of polycarbonyl compounds. Ihmels *et al*. probed the oxidation of a series of heterocyclic α-diazoketones using dimethyl dioxirane (DMD) as the oxidising agent of choice.[302] Substrates under examination included furans, thiophenes and pyridines (**Scheme 1.137**). Oxidation of the α-diazoketone **419** provided glyoxal **420** in pure form (>95% yield), in spite of the presence of an oxidisable nitrogen atom for the pyridine substrate and a sulfur atom in the case of thiophene substrates. The glyoxal **420** was characterised as the diazanaphthalene **421** (quinoxaline) by reaction with 1,2-diaminobenzene in ethanol at room temperature.



Scheme 1.137

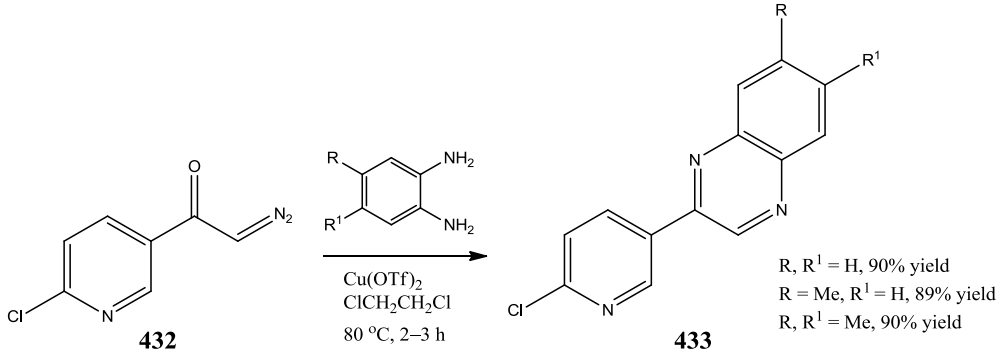
The enantioselective preparation of *N*-protected α-amino glyoxals has been reported by McKervey and Ye (**Scheme 1.138**).[303,304] Oxidation of the corresponding α-diazoketones **422-425** using DMD generated the enantiopure glyoxals **426-429**. In this work, it was imperative

to protect the amino functionality of the amino acid precursor, as without *N*-protection, the ensuing glyoxals are expected to be subject to spontaneous polymerisation. In addition, the glyoxal **429** was condensed with either 2,3-diaminobenzene or 2,3-diaminopyridine to furnish the optically active quinoxaline **430** or azaquinoxaline **431** respectively.



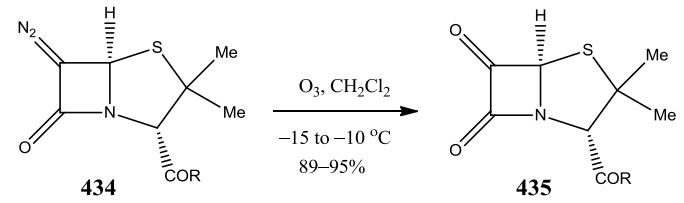
Scheme 1.138

Yadav and co-workers have devised a method permitting a one-pot synthesis of quinoxalines from α-diazoketones and diamino compounds using $Cu(OTf)_2$ as catalyst (**Scheme 1.139**).[305] It was found that $Rh_2(OAc)_4$ was as effective as the copper catalyst for these reactions (5 mol% *cf.* 10 mol% loading), although this can be considered a higher catalyst loading than conventional rhodium-catalysed transformations. While the trapping of glyoxal type compounds as their corresponding quinoxaline derivatives has previously been reported, this is the first published example of direct coupling of α-diazoketones and diamines to provide potential biologically active quinoxaline analogues in a one-step process. Substrate scope mainly included aromatic and alkyl compounds but a pyridine α-diazoketone **432** was also utilised in this operation to prepare the quinoxalines **433**. Recently, Ley and co-workers have developed a safe and reliable preparation of quinoxalines from terminal α-diazoketones using $Cu(OTf)_2$ and 1,2-diamines through the use of flow reactor conditions.[306] Numerous acyclic and phenyl derivatives, as well as thiophene were employed as substrates in this process.



Scheme 1.139

Oxidation of primary α-diazoketones using ozone has been carried out by Ursini on 6-diazo-aminopenicillinates **434**.[307] Formation of the diketone product **435** was achieved in a highly efficient manner (**Scheme 1.140**).



434 **435**

R = Bn, CH_2, *p*-$NO_2C_6H_4$
CH_2CCl_3, CH_2OCOt-Bu

Scheme 1.140

1.5.6.3 1,2-Hydride shift and β-elimination

In addition to the Wolff rearrangement, other rearrangements of α-diazocarbonyl compounds are possible such as 'β-hydride elimination', although a 1,2-hydrogen shift/β-hydride migration is a more accurate definition of the process. The 1,2-alkyl shift and β-elimination reactions are also noteworthy rearrangement pathways. The 1,2-hydrogen shift rearrangement is generally viewed as a competing side-reaction in α-diazocarbonyl transformations where other reaction pathways are anticipated. Fox has reported that methine hydrogens show a higher propensity towards β-hydride migration than methylene hydrogens while β-hydride migration is rare in the case of methyl hydrogens,[288] in accordance with earlier observations by Taber (**Figure 1.11**).[308]

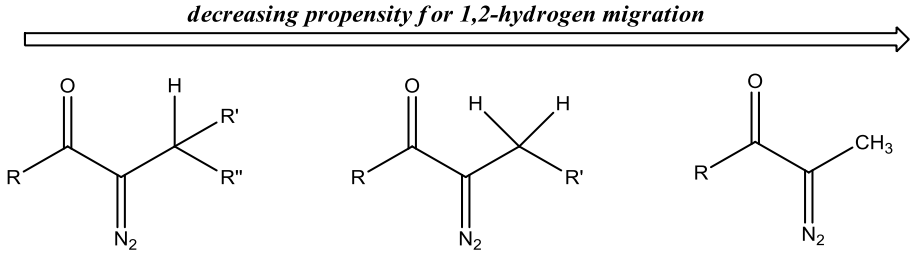
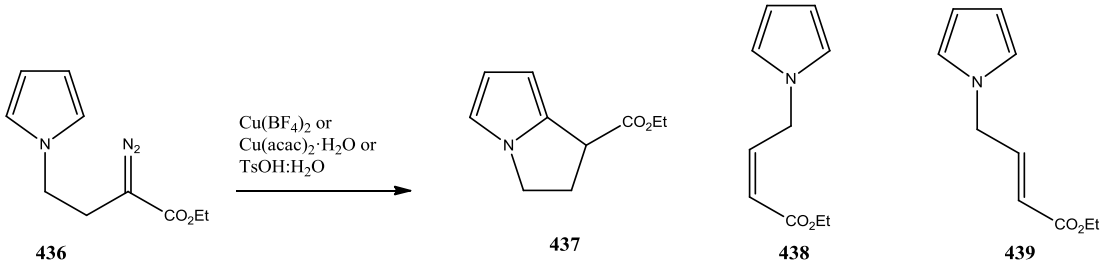


Figure 1.11[288]

There is little scope for further structural modification of products compared to other transformations of α-diazocarbonyl substrates, though it can be used to provide additional unsaturation to the compound. The generation of β-hydride shift products from transition metal catalysis of diazo compounds has been reported,[309-313] though both temperature and catalyst control can minimise their formation. Hashimoto has demonstrated complete elimination of a β-hydride migration pathway at low temperatures in the generation of cyclopentanones,[313] while it has been noted in work by Taber that electronic differences in the rhodium(II) catalyst can tend to favour formation of a 1,2-hydride shift product.[308,314] Catalysts possessing strongly electron-withdrawing ligands, *e.g.* $Rh_2(pfb)_4$ and $Rh_2(tfa)_4$, are particularly efficient for this process due to the highly reactive and electron-deficient metallocarbenoid generated. Moreover, 1,2-hydrogen migration from photochemical reactions of diazo substrates is well precedented.[315-320]

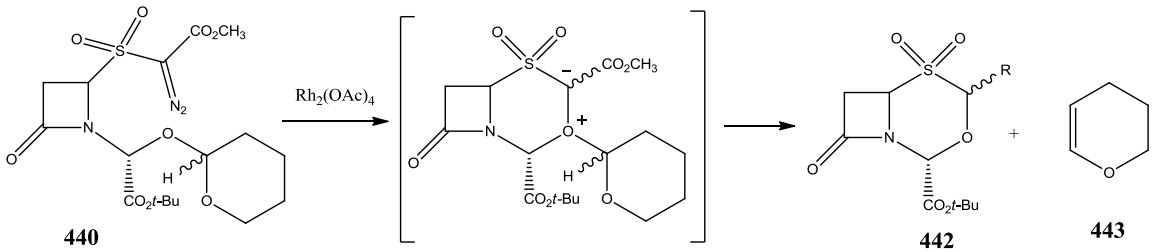
Reports of the 1,2-hydride shift in heterocyclic-containing α-diazocarbonyls have appeared, however, examples of these processes are few in number in comparison to the presence of [1,2]-hydride shift products derived from acyclic α-diazocarbonyl substrates. In 1983, Muchowski reported the first examples of intramolecular carbenoid insertion into the pyrrole ring.[131] In these studies, cyclisation of α-diazoester **436** predominantly provided the desired bicyclic product **437** in addition to *cis* and *trans* alkenes **438** and **439**, arising from a competitive β-hydride migration. Interestingly, reaction of **436** in the presence of *p*-toluenesulfonic acid solely generated the β-hydride migration products with complete absence of C–H insertion product **437**.



Ratio 437 : 438 : 439			
$Cu(BF_4)_2$	70	17	13
$Cu(acac)_2 \cdot H_2O$	81	0	19
$TsOH:H_2O$	0	53	47

Scheme 1.141

Crackett and co-workers have investigated tandem intramolecular oxonium ylide formation/β-elimination of highly functionalised β-lactam-derived α-diazo-β-sulfonylacetates **440**, with a view to assembling oxacephams (**Scheme 1.142**).[157] Initial formation of the oxonium ylide **441** and subsequent elimination afforded the desired oxacephams **442** as a mix of diastereomers in 44–63% yield, with a pyran derivative **443** observed as a side product *via* a β-elimination pathway. In addition, Fox has reported generation of β-hydride migration products from the reactions of cyclic α-diazocarbonyl compounds using $Rh_2(tfa)_4$ as catalyst, as previously discussed (**Scheme 1.128**).[288]



R = β-CO_2CH_3, 47% yield
R = α-CO_2CH_3, 16% yield

Scheme 1.142

1.6 Synthetic routes to pyridine-containing α-diazocarbonyl compounds

A comprehensive review of the literature demonstrates that pyridine-containing α-diazocarbonyl compounds are generally accessible by four principal synthetic routes:

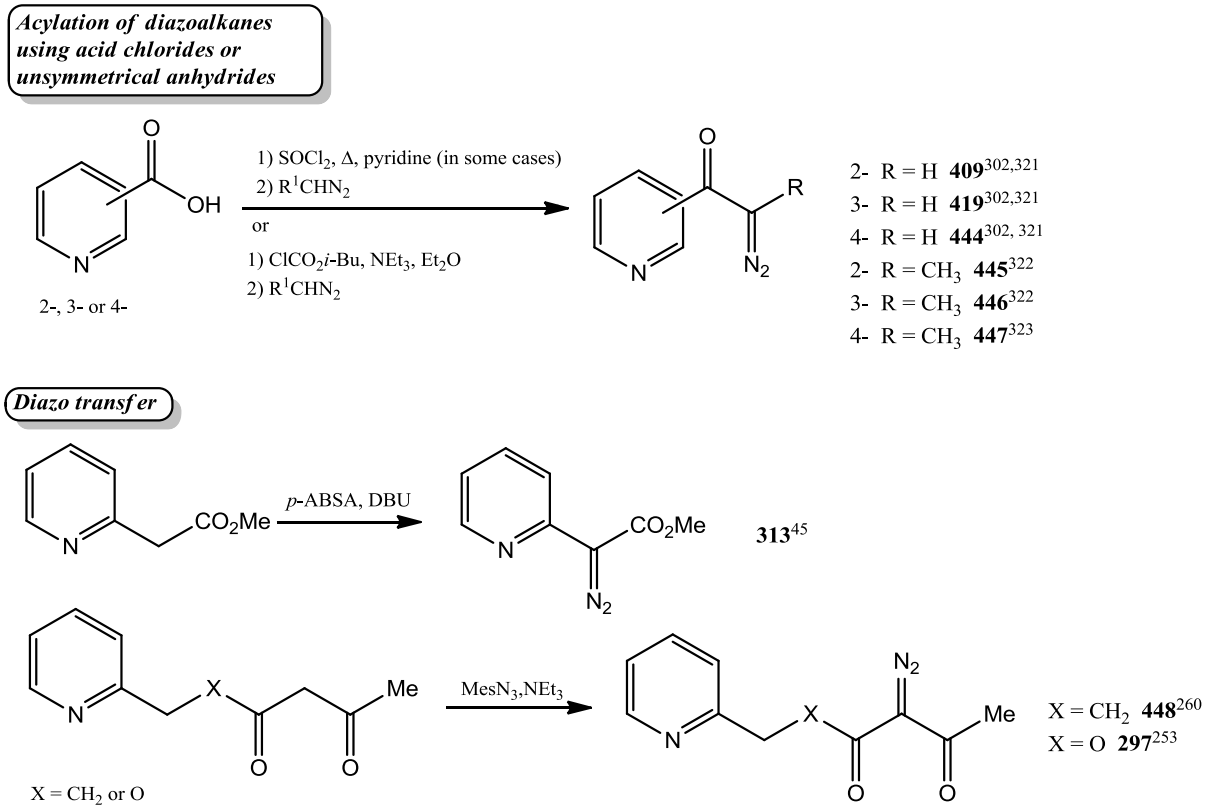
a) Acylation of diazoalkanes using acid chlorides[302,321,322] or unsymmetrical anhydrides[323]

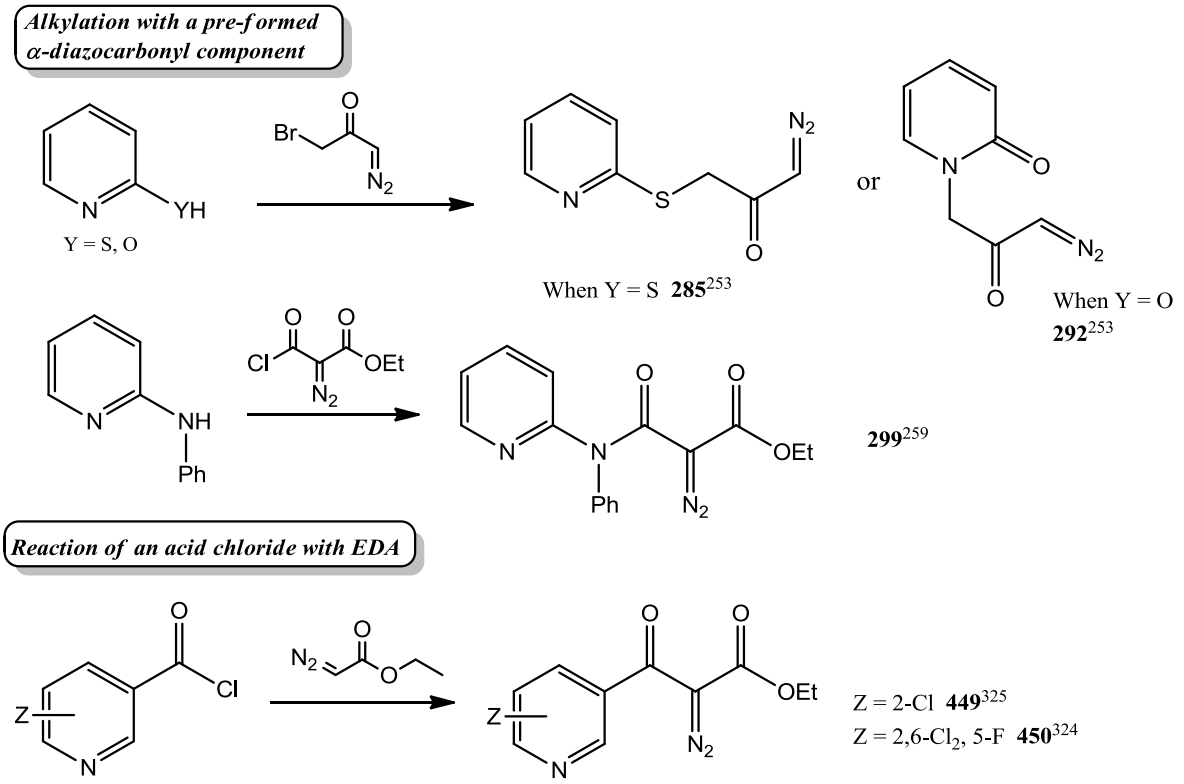
b) Diazo transfer to an activated methylene group[45,253,260]

c) Reaction of a pyridinethiol, hydroxypyridine or aminopyridine with a pre-formed α-diazocarbonyl component[253,259]

d) Generation of α-diazo-β-ketoesters in one-pot by reaction of an acid chloride with ethyl diazoacetate[324,325]

A summary of the synthetic strategies, as well as the literature precedent for the preparation of compounds **285**, **292**, **297**, **299**, **313**, **409**, **419** and **444-450** is illustrated below (**Scheme 1.143**). The aim of presenting this synopsis of pyridine-containing α-diazocarbonyl syntheses is to establish possible strategies for use in our work prior to undertaking generation of these compounds. Many of the routes have previously been discussed in this chapter and the majority of these approaches are explored throughout the course of the second chapter in this work.





Scheme 1.143

1.7 Conclusion

Heterocyclic systems constitute the largest group of organic compounds and are vital components in many aspects of organic, medicinal and applied chemistry. The generation of elaborate heterocycles in an expeditious high yielding manner represents a valuable target for synthetic organic chemists both in academia and the pharmaceutical industry. This overview has highlighted that heterocyclic α-diazocarbonyl systems are versatile synthetic building blocks, able to undergo a vast array of transformations in high chemo-, regio-, diastereo- and enantioselectivity. Despite the variety of reaction pathways possible, selectivity can be achieved through catalyst, substrate and reaction condition control. These compounds should continue to attract considerable attention in the wide-ranging area of heterocyclic synthesis.

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Chapter 2

Preparation of Pyridine-Containing α-Diazocarbonyl Compounds and Investigation of Their Reactivity

I have not failed. I've just found 10,000 ways that won't work.

Thomas Edison, Inventor, Scientist and Businessman (1847-1931)

"Two little mice fell in a bucket of cream. The first mouse quickly gave up and drowned. The second mouse, wouldn't quit. He struggled so hard that eventually he churned that cream into butter and walked out. Gentlemen, as of this moment, I am that second mouse."

Frank W. Abagnale Snr., 'Catch Me If You Can' (2002)

Contents

2.1 Introduction

2.1.1 Heterocycles in medicinal chemistry

Heterocycles display a remarkable range of diversity and biological efficacy as these compounds are vital components in vitamins, antibiotics and in biological processes as porphyrins, cytochromes, co-enzymes and nucleosides.[1] The pyridine, pyridone and azepine/diazepine moieties are crucial sub-units for an array of natural products and pharmaceutically active drugs, treating a broad spectrum of conditions; type II diabetes, chronic myeloid leukemia, ovarian and colon cancer, Parkinson's disease, epilepsy, schizophrenia and insomnia. The structures and functions of some of these drugs are shown below (**Figure 2.1**).

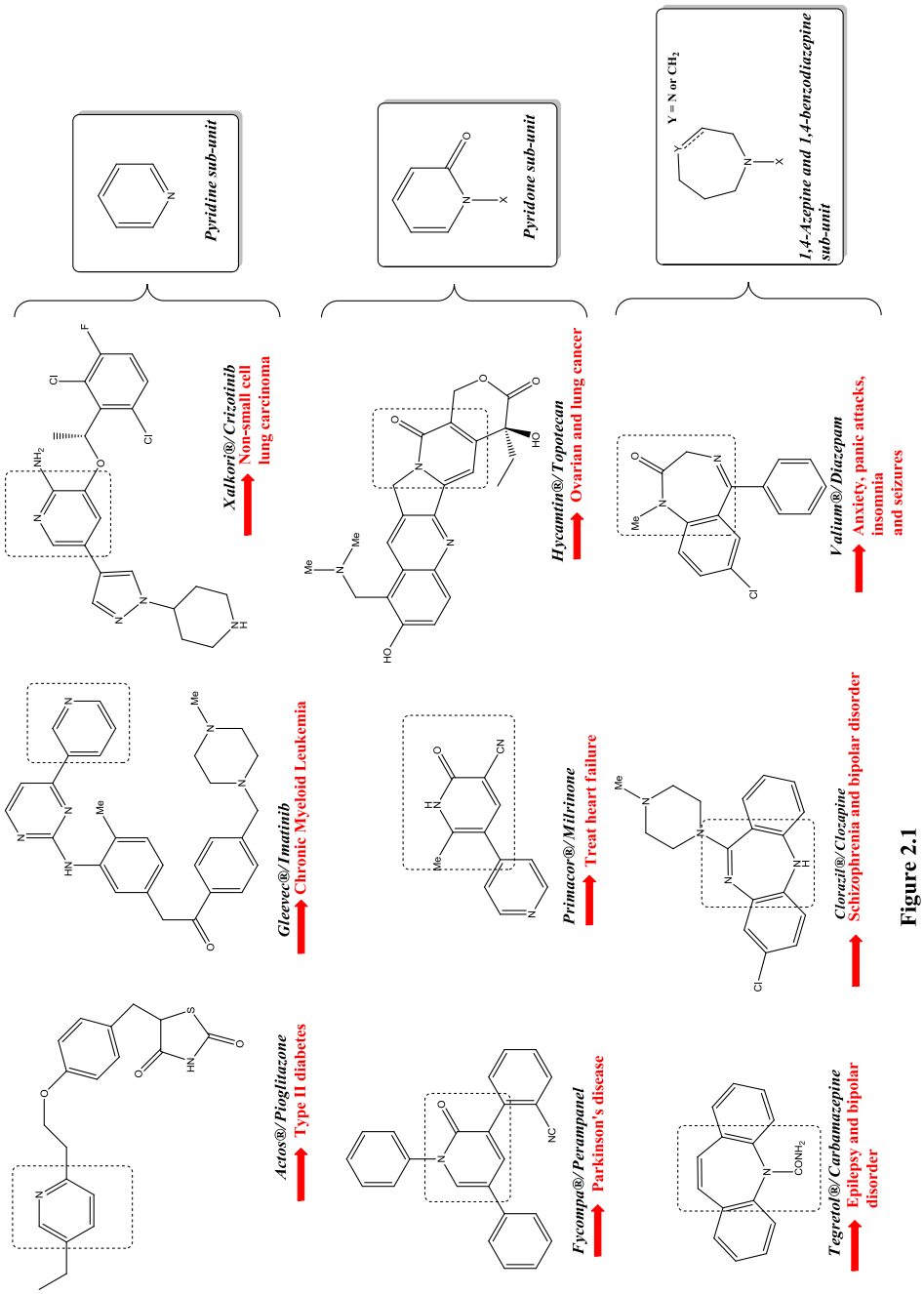
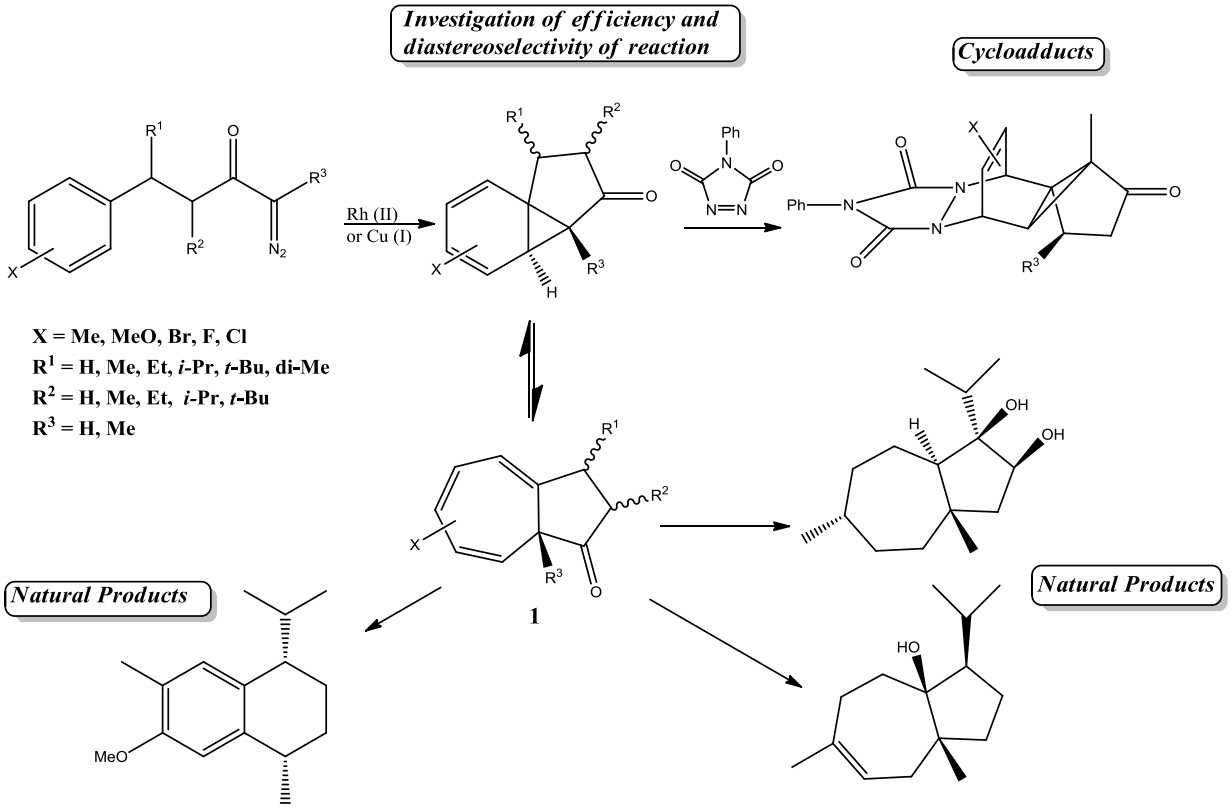


Figure 2.1

2.1.2 Introduction to α-diazocarbonyl chemistry

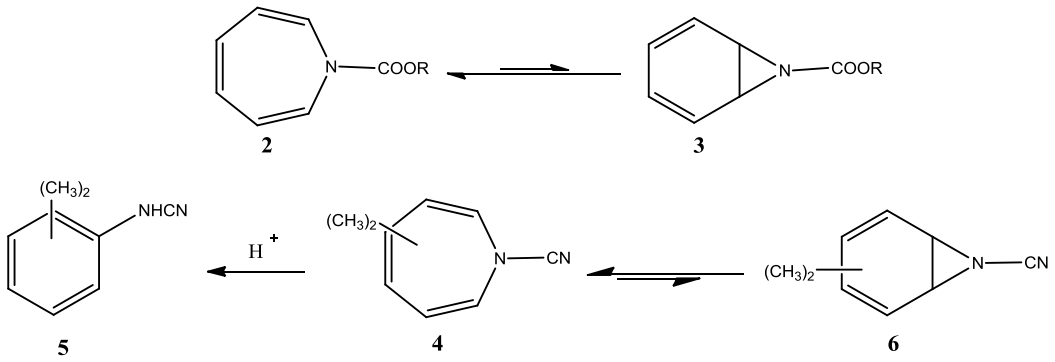
Rhodium- and copper-catalysed aromatic addition reactions of α-diazoketones, *i.e.* the intramolecular Buchner reaction, have been extensively studied within the Maguire research group and this methodology has served to generate useful scaffolds in the formation of a range of natural product derivatives and cycloadducts (**Scheme 2.1**).[2-12] Such compounds arise from simple functional group transformations of the cycloheptatriene tautomer or by trapping the norcaradiene tautomer in a [4+2]-cycloaddition reaction. Other aspects of this reaction have been investigated, including introduction of various electron-donating substituents (EDGs) and electron-withdrawing substituents (EWGs) on the ring, alkyl and aryl substitution at the α- and β-position of the linker chain and the enantioselective synthesis of the cycloheptatriene, norcaradiene and cycloadducts.[8-19] This research has illustrated the effect these parameters have on the position and extent of the norcaradiene/cycloheptatriene equilibrium, as well as the efficiency and diastereoselectivity of the reaction.



Scheme 2.1

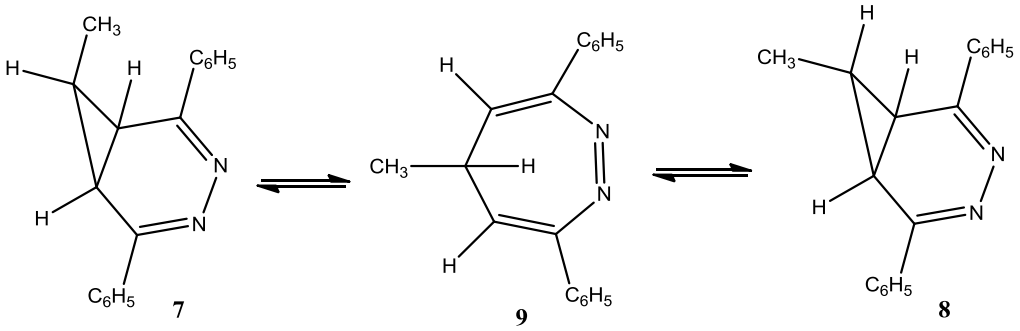
One of the most interesting structural features of the azulenone system **1** above (**Scheme 2.1**) is the dynamic interconversion between the norcaradiene and cycloheptatriene isomers which exist in equilibrium.[20] Related dynamic interconversions have also been reported in rings systems containing nitrogen atoms.

It has been observed that a monocyclic azepine system exists in tautomeric equilibrium with the corresponding bicyclic intermediate, provided an electron-withdrawing group (EWG) is attached to the nitrogen (**Scheme 2.2**).[21] The azepine **2** was observed as the favoured product with a limited amount of benzene imine **3** observed. It was also noted that the *N*-cyanoazepine **4** can rearrange under acidic conditions to form phenyl cyanamide **5**, with isomerisation conceivably proceeding *via* azanorcaradienes **6**.[22]



Scheme 2.2

In a scenario where more than one nitrogen atom is part of the ring system, the presence of nitrogen atoms at positions 3- and 4- of the norcaradiene ring leads to stabilisation of the bicyclic structure, thus resulting in the existence of the norcaradiene as the most thermodynamically stable form (**Scheme 2.3**).[23] This is especially evident with the 2,5-diphenyl-substituted-3,4-diazanorcaradienes, which apparently interconvert between *cis* **7** and *trans* **8** isomers through valence-tautomerisation with the diazacycloheptatriene **9**.



Scheme 2.3

Based on our experience in the synthesis of azulenones **1** through the intramolecular aromatic addition of α-diazoketones, extension to the synthesis of azepines and azanorcaradienes can be envisaged through the hitherto unprecedented use of pyridyl α-diazoketones in place of the earlier phenyl α-diazoketones (**Scheme 2.4**).

2.2 Objectives

The primary objective of this work was to determine whether pyridyl-containing α-diazoketones of general structure **10** undergo intramolecular aromatic addition analogous to the intramolecular Buchner reaction extensively studied with simple aryl derivatives.

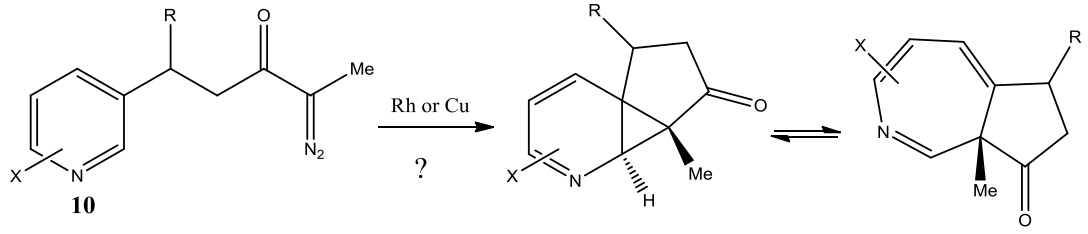
To achieve this, the specific objectives were;

- To design and synthesise a series of novel pyridine-containing α-diazocarbonyl compounds, both ketones and esters.

- Establishing a reliable and robust route to these pyridyl-containing α-diazocarbonyl compounds was a priority. In addition, establishing the scope and stability of the novel α-diazocarbonyl compounds was essential as there are very limited reports to date of pyridine-containing α-diazocarbonyl compounds.

- To investigate the reactivity of these novel pyridine α-diazocarbonyl compounds using transition metal catalysis.

- To determine whether intramolecular aromatic addition occurs analogous to the pathways seen with the phenyl α-diazocarbonyl compounds (**Scheme 2.4**).



Scheme 2.4

This chapter will describe the synthesis and reactivity of novel pyridine-containing α-diazoketones and esters.

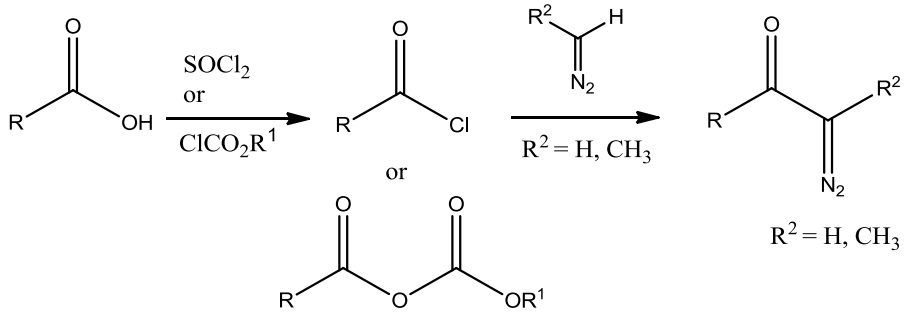
2.3 Synthesis of α-diazoketones

2.3.1 Background and approaches to α-diazoketones

The preparation of α-diazocarbonyl compounds can be accomplished by two main routes; acylation of diazoalkanes, and diazo transfer using a sulfonyl azide reagent.

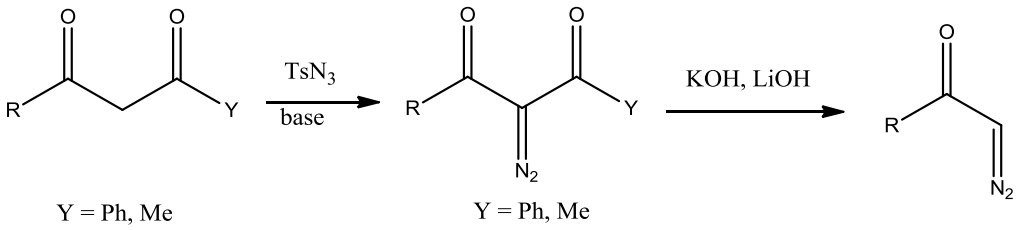
1) Activation of the pyridine substituted carboxylic acid to form a reactive intermediate (acid chloride[9,10] or unsymmetrical anhydride[24,25]), followed by acylation of

diazomethane, trimethylsilyldiazomethane or diazoethane to generate the α-diazoketone (**Scheme 2.5**).



Scheme 2.5: Acylation of diazoalkanes

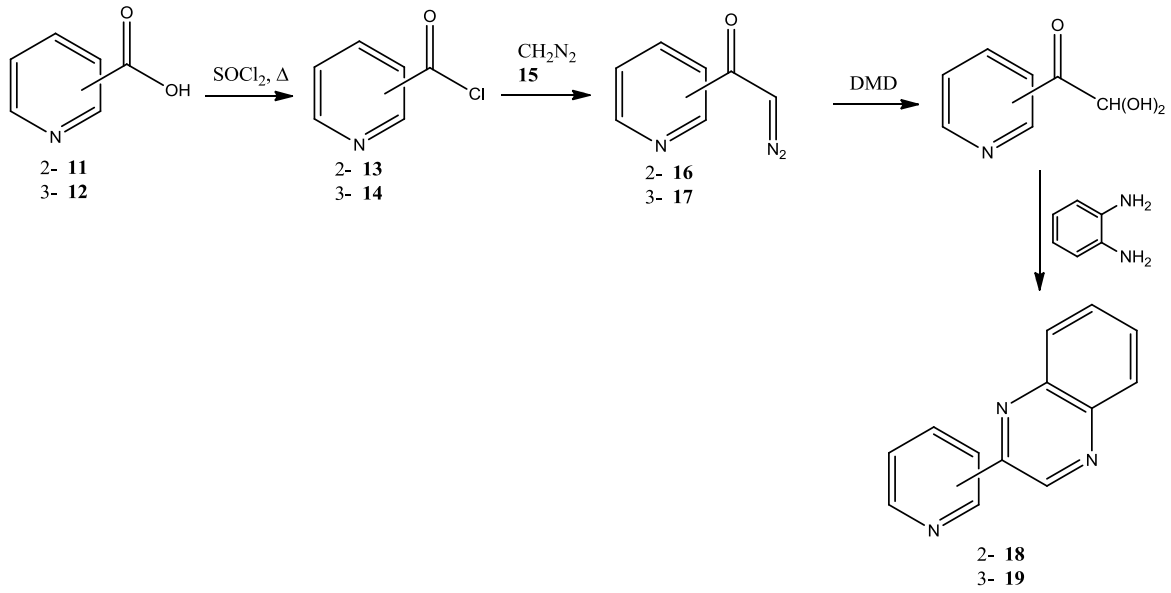
2) Diazo transfer methodology to activated methylene groups, followed by base-induced deacylation to furnish α-diazoketones (**Scheme 2.6**).



Scheme 2.6: Preparation of α-diazoketones *via* diazo transfer[26,27] and deacylation[28]

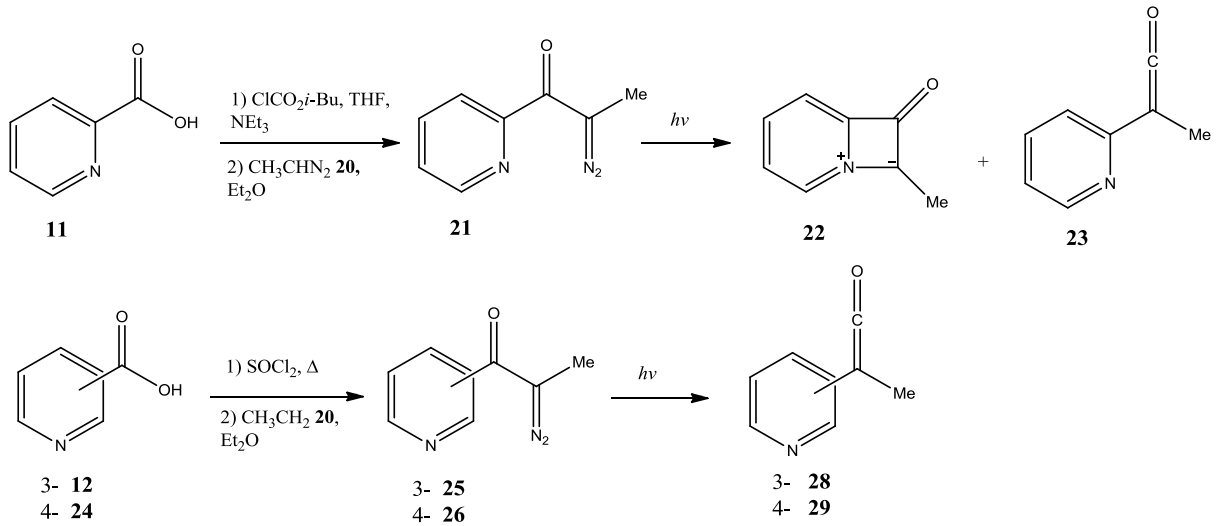
While the reactions of α-diazocarbonyl compounds have been extensively studied in the literature, very few examples involving formation of pyridine-containing α-diazoketones and their subsequent transformations have been reported.

Ihmels and co-workers have succeeded in generating pyridine-containing α-diazoketones from acid chlorides and diazomethane **15** in low yields; the acid chlorides **13** and **14** were synthesised from the corresponding picolinic **11** and nicotinic **12** acids using thionyl chloride with heating under reflux conditions (**Scheme 2.7**).[29] The α-diazoketones **16** and **17** were subsequently oxidised to afford glyoxals using dimethyldioxirane (DMD) and fully characterised as quinoxalines **18** and **19** by further reaction with *o*-phenylenediamine.



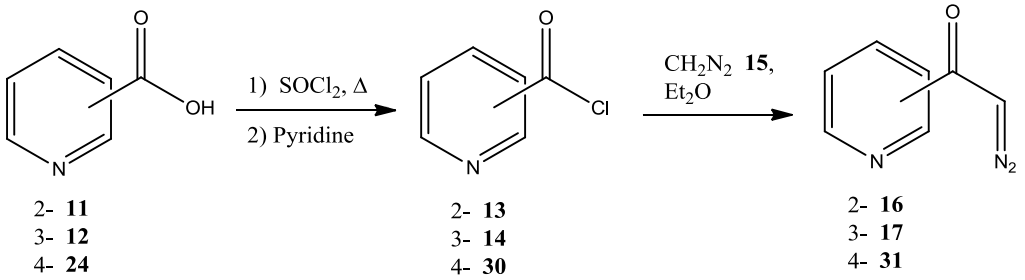
Scheme 2.7

Tidwell has utilised the mixed anhydride coupling method using isobutyl chloroformate to prepare the unsymmetrical anhydride, with subsequent acylation of diazoethane **20** generating the pyridine α-diazoketone **21** (**Scheme 2.8**).[30] Photolytic reaction of **21** led to formation of an azacyclobutanone ylide **22** and the corresponding ketene **23**. Pitters and co-workers have reported the synthesis of the corresponding 3- and 4-pyridyl α-diazoketones **25** and **26** using acid chlorides and diazoethane **20** in the pursuit of generating the analogous ketenes **28** and **29**.[31]



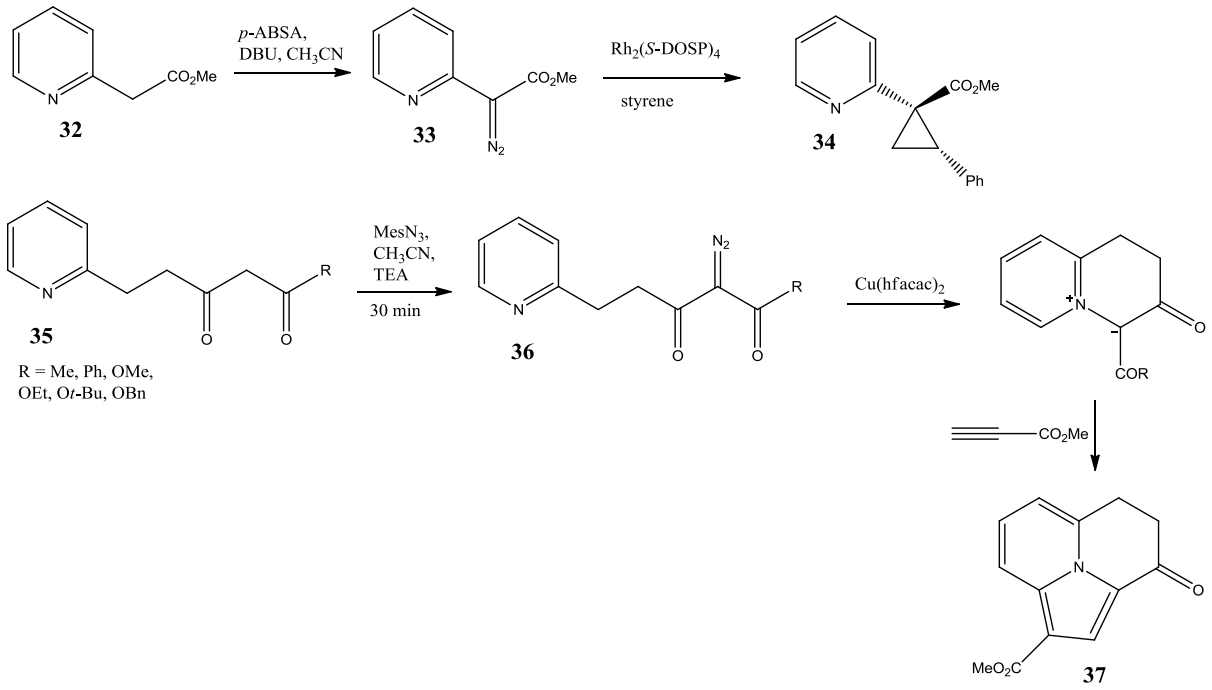
Scheme 2.8

Queguiner has prepared α-diazoketones **16**, **17** and **31** using the acid chloride route. A key point in this work was that an excess of pyridine was added to the crude acid chlorides **13**, **14** and **30** prior to purification by vacuum distillation, which presumably prevents formation of the quaternary ammonium salt (**Scheme 2.9**).[32]



Scheme 2.9: Formation of pyridine α-diazoketones *via* acid chlorides with addition of pyridine prior to purification by vacuum distillation

Pyridine-containing α-diazo-β-ketoesters **33** and **36** have been prepared through diazo transfer to suitably activated pyridine substrates using *p*-ABSA and mesitylenesulfonyl azide ($MesN_3$) (**Scheme 2.10**). These heterocyclic α-diazocarbonyl compounds were subsequently reacted with transition metal catalysts in intermolecular cyclopropanations carried out by Davies[33] and tandem azomethine ylide formation/1,3-dipolar cycloaddition reactions reported by Oku and co-workers (**Section 1.5.4.1** and **Section 1.5.3.5**).[34]

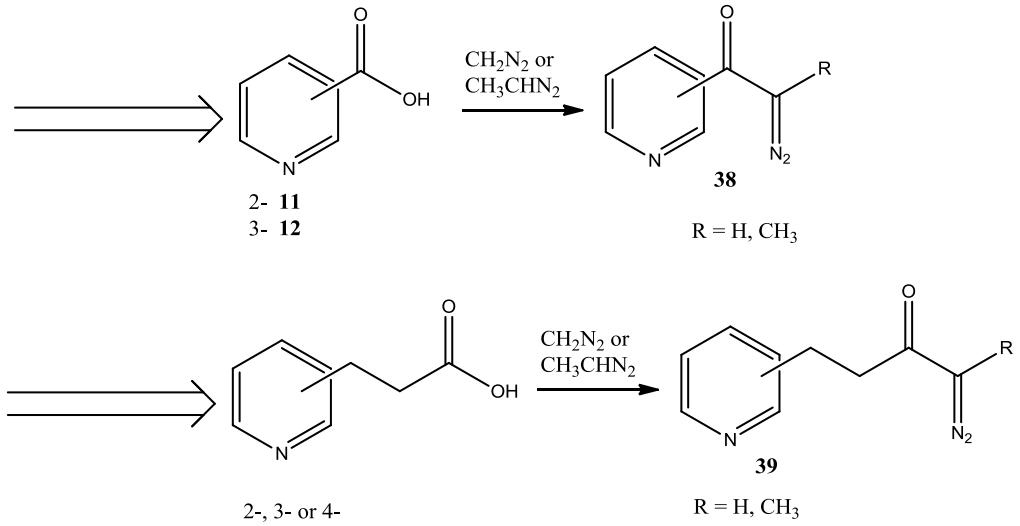


Scheme 2.10: Pyridine α-diazocarbonyl compounds prepared using diazo transfer approach

2.3.1 Synthesis of α-diazoketones and α-diazo-β-ketoesters *via* diazoalkane acylation

2.3.1.1 Background

The first α-diazoketone targets in this work were of general structure **38** or **39** (**Scheme 2.11**). In order to generate the pyridine-containing α-diazoketones, the most convenient route involved initial preparation of carboxylic acids. The short-chain 2- and 3-substituted pyridine carboxylic acids **11** and **12** were commercially available but the 2-, 3- and 4-pyridylpropanoic acids required as precursors had to be synthesised and this is discussed below.



Scheme 2.11

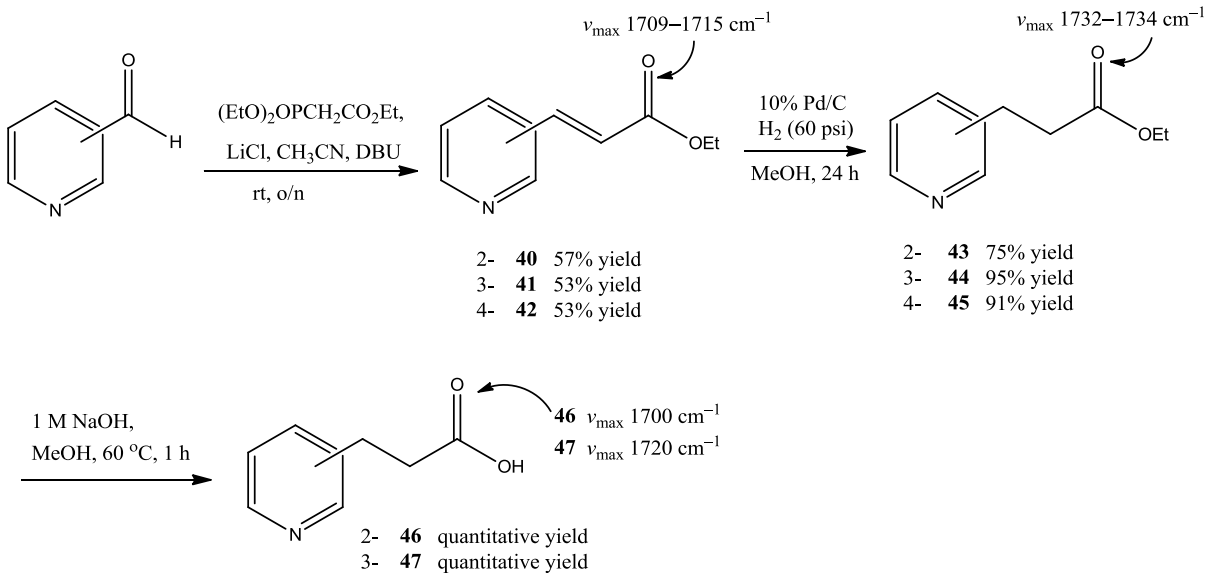
2.3.1.2 Early efforts in the synthesis of pyridine-containing α-diazoketones

2.3.1.2.1 Generation of pyridyl carboxylic acids

Carboxylic acids are useful precursors in the synthesis of α-diazoketones, with most methods of preparation involving activated acids as acylating agents for diazoalkanes. The synthetic approaches to prepare the appropriate carboxylic acids involved conversion of unsubstituted pyridine aldehydes to the corresponding α,β-unsaturated esters *via* Horner-Wadsworth-Emmons methodology or alternatively, formation of the α,β-unsaturated acids by Knoevenagel reaction.

Using the Horner-Wadsworth-Emmons procedure,[35] commercially available 2-, 3- and 4-substituted pyridinecarboxaldehydes were reacted with triethyl phosphonoacetate, lithium chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile to furnish the acrylate esters **40-42** in good yields following purification by column chromatography (**Scheme 2.12**). Preparation of compounds **40-42** has been reported[36-40] but were not synthesised previously using this method. The next step involved hydrogenation of the α,β-unsaturated esters to give the saturated analogues following a method described by Hallinan[36] and using a slight modification of replacing ethanol with methanol as the solvent. Reaction conditions involved methanol as solvent and palladium on carbon as catalyst under hydrogen at 60 psi, for 24 h at room temperature. Completion of the hydrogenation was confirmed by ^{1}H NMR

spectroscopy, infrared spectroscopy and TLC analysis; the saturated esters **43-45** were formed in high yields. Synthesis of the carboxylic acids was completed by hydrolysis of the esters using aqueous sodium hydroxide in methanol at 60 °C for 1 h following a method outlined by Kato.[41] This procedure was applied to the 2- and 3-substituted esters **43** and **44** to furnish the corresponding acids **46** and **47** in quantitative yields. The spectral data obtained for compounds **40-47** were in accordance with those previously described in the literature.[37,39,42-45]

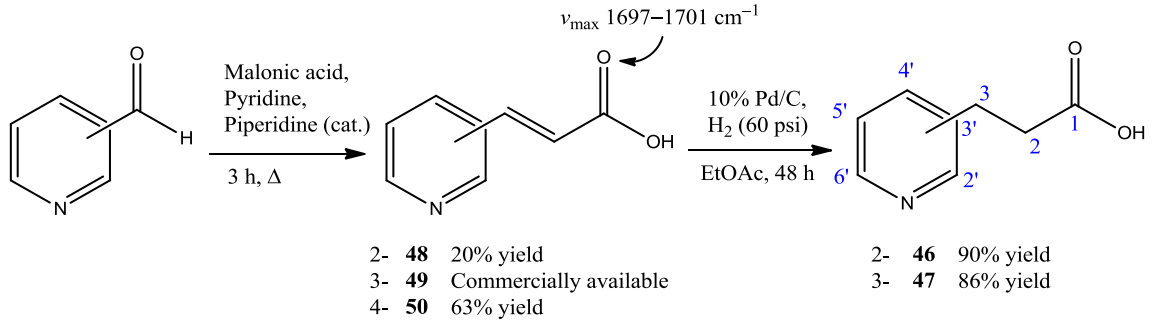


Scheme 2.12: Horner-Wadsworth-Emmons route; synthesis with characteristic infrared frequencies

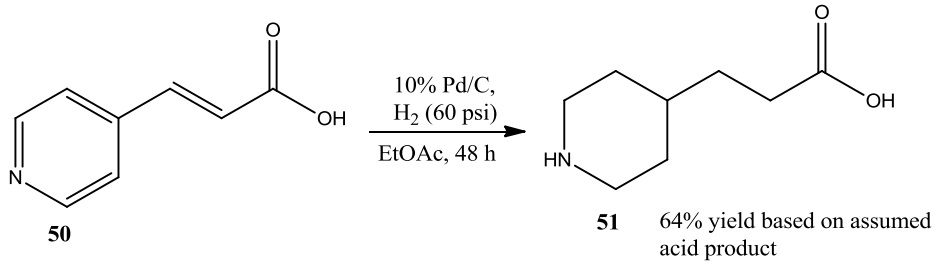
An alternative route to the carboxylic acids involved the Knoevenagel reaction using 2- and 4-pyridinecarboxaldehydes with malonic acid, pyridine and piperidine following a literature procedure (**Scheme 2.13**).[46] This protocol was applied to 2- and 4-substituted aldehydes only as 3-pyridineacrylic acid **49** was commercially available. While the 2-pyridineacrylic acid **48** was isolated in a low yield (20%), the isomeric acid **50** was obtained in 63% yield. The infrared spectrum of the acids **48** and **50** contained broad peaks at ν_{max} 2380 and 1891 cm^{-1} in addition to the carbonyl band and there was literature support for this observation in both compounds,[46,47] as well as the 3-pyridineacrylic acid **49**.[46,48] Hydrogenation of acids **48** and **44** following the literature conditions afforded the saturated acids **46** and **47** in 90% yield for **46** and 86% yield for **47**,[37] though hydrogenation of the 4-substituted acid **50** did not proceed satisfactorily. The hydrogenation conditions comprised using ethyl acetate as solvent at a pressure of 60 psi of hydrogen and the reactions were deemed to be complete after 48 h following ^{1}H NMR spectroscopy and TLC analysis. Hydrogenation of pyridineacrylic acids involved slightly longer reaction times than required for unsaturated esters which may reflect the change in solvent from methanol to ethyl acetate.

The only reported hydrogenation of **50** by Merck indicated reduction of both the side-chain and the pyridine ring to generate a piperidinepropanoic acid·HCl salt using dichloromethane/methanol as solvent.[49] This illustrates that hydrogenation of this substrate

under standard conditions is not straightforward and the hydrogenation proceeds beyond saturation of the alkene. Proton NMR analysis of the crude product is consistent with the over-hydrogenated product 3-(piperidin-4-yl)propanoic acid **51** potentially as the internal salt as this was isolated as a white solid soluble in water (**Scheme 2.14**).



Scheme 2.13: Strategy employing Knoevenagel route



Scheme 2.14: Attempted hydrogenation of 50

The pyridinepropanoic acids **46** and **47** were successfully prepared using both using the three-step method *via* the Horner-Wadsworth-Emmons procedure and the two-step approach utilising the Knoevenagel protocol. Overall, the yields were more reliable using the Horner-Wadsworth-Emmons method to synthesise multigram quantities for subsequent generation of α-diazoketones.

Examination of substrate **47** by $^{1}H–^{13}C$ HSQC and $^{1}H–^{13}C$ HMBC analysis (see *Appendix V*) facilitated definitive assignment of signals for both methylene groups, $C(2)H_2$ and $C(3)H_2$, in the ^{1}H NMR and ^{13}C NMR spectra. The assignment of these signals prior to this work was ambiguous as the only pertinent literature data described the predicted ^{1}H and ^{13}C NMR values for **47** by Griffiths.[50] The direct correlation using a $^{1}H–^{13}C$ HSQC experiment demonstrated that the signal located at δ_H 2.70 ppm correlates with the signal at δ_C 33.9 ppm, while the triplet identified at δ_H 3.01 ppm is associated with a value of δ_C 27.1 ppm (**Figure 2.2**). Further investigation using $^{1}H–^{13}C$ HMBC experiment illustrates an indirect correlation of signal at δ_H 3.01 with the aromatic hydrogens on the pyridine ring, C(2')H, C(4')H and C(6')H, located at δ_C 140.7, 142.6 and 144.2 ppm. This successfully identifies the signals at δ_H 3.01 and δ_C 27.01 as being associated with the methylene group $C(3)H_2$, as illustrated in the numbering scheme above (**Scheme 2.13**). The $^{1}H–^{13}C$ HMBC connectivities also highlights an indirect correlation between the signals at δ_H 2.70 ppm and the quaternary

carbonyl carbon, C(1)=O, located at δ_C 173.2 ppm. Therefore, the signals at δ_H 2.70 ppm and δ_C 33.9 ppm are ascribed to C(2)H_2, as illustrated below (**Figure 2.2**). This analysis is the basis for assignment of signals for the two methylene groups, C(2)H_2 and C(3)H_2 in both ^{1}H and ^{13}C NMR spectroscopy for the saturated long-chain esters, carboxylic acids and α-diazoketones subsequently investigated.

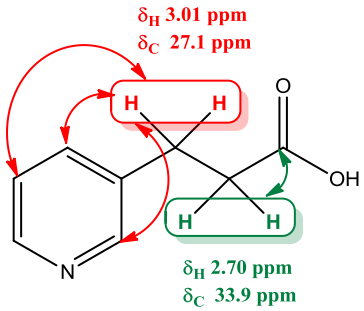


Figure 2.2: ^{1}H–^{13}C HSQC (500 MHz and 125.8 MHz, DMSO-*d*$_6$) of values of 47 and ^{1}H–^{13}C HMBC (500 MHz and 125.8 MHz, DMSO-*d*$_6$) connectivities of 47

2.3.1.2.2 Synthesis of pyridine-containing α-diazoketones via *acylation of diazoalkanes*

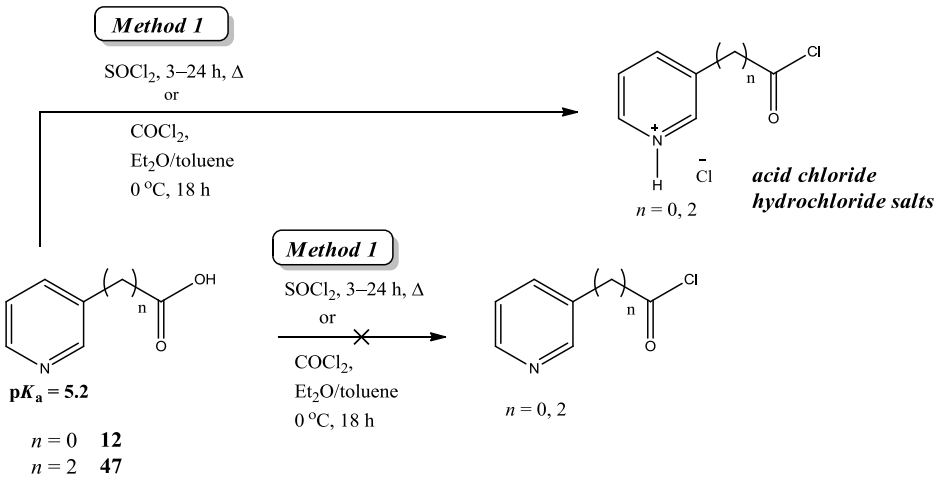
The carboxylic acids **46** and **47**, along with commercially available picolinic **11** and nicotinic acid **12** were substrates for the attempted preparation of α-diazoketones using a variety of acylation methods. The main substrate studied in these reactions was 3-(pyridin-3-yl)propanoic acid **47**, while acids **11**, **12** and **46** were explored for some of the acylation methods. The approaches investigated for preparation of α-diazoketone included;

1) Acid chloride formation[9,10]
2) Unsymmetrical anhydride[25,51]
3) DCC and DIC coupling[24,52]
4) Cyanuric chloride coupling[53]
5) NBS/PPh_3 coupling[54]

Since it was reported in the literature that pyridine acid chlorides can be formed under standard conditions,[55] it was assumed at the outset that this procedure would prove a straightforward step in the synthesis of the α-diazoketones. Employing standard conditions previously optimised in our laboratory [thionyl chloride (10 equiv.) and carrying out the reaction at reflux,[10,11,16]] there was a noticeable difficulty in forming the pyridine acid chloride from acid **47** in spite of varying the length of the time for the reaction from 3–24 h. In all cases, there was an absence of the distinctive acid chloride stretch in the infrared spectrum (~1780–1800 cm^{-1}). On replacing chlorinating agent from thionyl chloride to oxalyl chloride, there was still no indication of formation of the acid chlorides using these milder conditions. Similarly, one attempt to convert **12** to the acid chloride proved unsuccessful. Katritzky has reported that pyridine acid chlorides are inherently unstable and difficult to

obtain,[56] providing further evidence that this particular route does not seem to be compatible with the substrates used here.

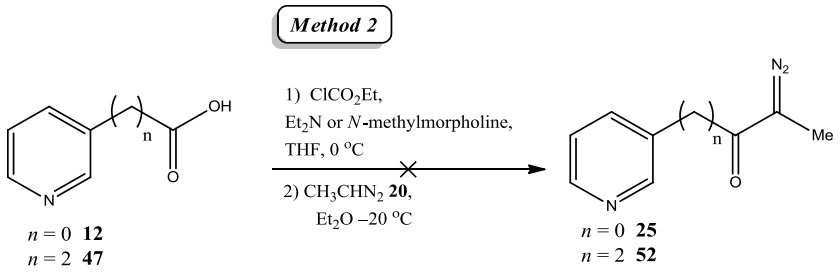
It has been observed that attempted syntheses of pyridine acid chlorides can result in the formation of acid chloride hydrochloride salts,[57] which may have an impact on their use in the synthesis of α-diazoketones (**Scheme 2.15**). While formation of acid chloride hydrochloride salts may be the case in this work, the salts were not identified and their formation is speculative (see **Scheme 2.24** for successful acid chloride formation).



Scheme 2.15

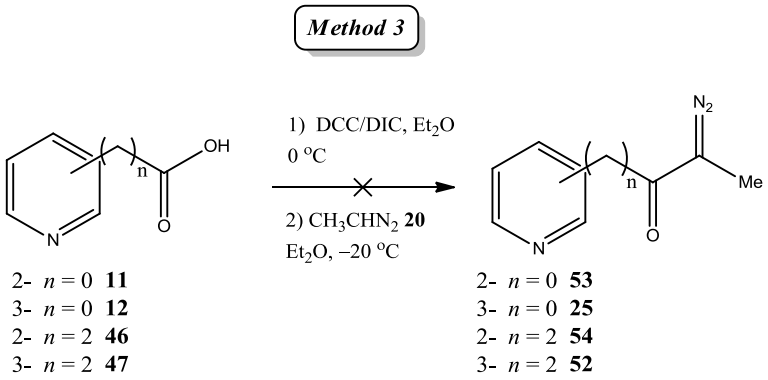
Since the acid chloride strategy did not prove fruitful with these substrates, a range of other methods were attempted to prepare pyridine-containing α-diazoketones. The unsymmetrical anhydride and DCC/DIC coupling routes have previously been employed to good effect in Maguire research group in the preparation of α-diazoketones,[25,52] though no pyridine substituted α-diazoketones were prepared using these procedures. The newer acylation techniques of using cyanuric chloride and NBS/PPh_3-mediated coupling have encouragingly reported formation of a pyridine substituted α-diazoketone **16** using these acylation methods.[53,54]

The unsymmetrical anhydride (Method 2) was the next procedure attempted and was applied to carboxylic acids **12** and **47**. The protocol involved the acid, ethyl chloroformate and triethylamine or *N*-methylmorpholine as base to generate the crude unsymmetrical anhydride intermediate, which was reacted with the freshly generated ethereal diazoethane **20** to prepare the α-diazoketone (**Scheme 2.16**). However, analysis of the crude product by ^{1}H NMR and infrared spectroscopy showed no indication of α-diazoketone formation for substrates **12** and **47**. The crude mixtures were subjected to chromatography but no discernible evidence of the successful synthesis of pyridine substituted α-diazoketones **25** and **52** was observed.



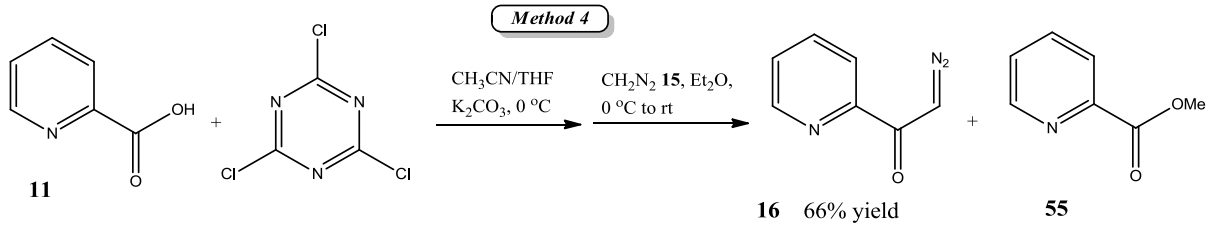
Scheme 2.16: Attempted unsymmetrical anhydride acylation of diazoethane 20

Coupling using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and *N*,*N*′-diisopropylcarbodiimide (DIC) (Method 3) was next carried out with each of the acids **11**, **12**, **46** and **47** (**Scheme 2.17**) and infrared spectroscopy of the crude products initially appeared to indicate the successful generation of α-diazoketones (ν_{max} ~2117 cm^{-1}). However, it was identified that stretching frequency initially assumed to correspond to the diazo functionality was attributed to the coupling reagent as the carbodiimide exhibits a characteristic infrared spectroscopic signature at ν_{max} 2117 cm^{-1}. Thus, the pyridine substituted α-diazoketones **25**, **52-54** were not successfully prepared *via* this method.



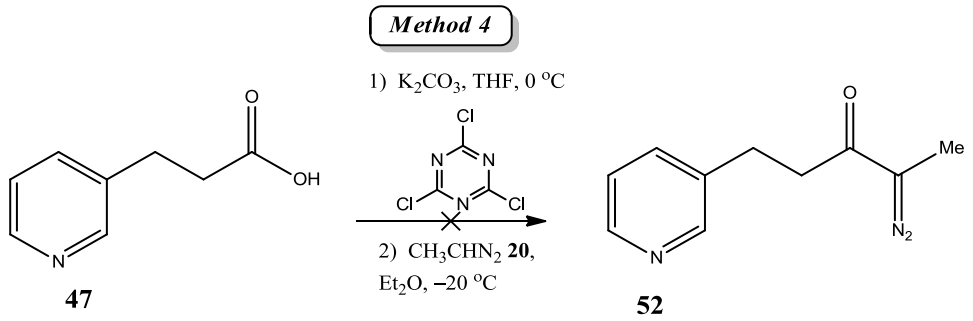
Scheme 2.17

The next efforts concentrated on the use of cyanuric chloride as a coupling reagent (Method 4), employing the reaction conditions outlined by Forbes and co-workers (**Scheme 2.18**).[53] The author has reported the formation of pyridine-containing α-diazoketone **16** using picolinic acid **11**. The conditions described used anhydrous potassium carbonate as base and cyanuric chloride as the activating agent in dry acetonitrile, with a tetrahydrofuran solution of picolinic acid **11** added slowly to the reaction mixture. Diazomethane **15** (2.7 equiv.) was added to the reactive intermediate in three equal portions at 0 °C and the reaction mixture was stirred overnight to provide α-diazoketone **16** after chromatographic purification. There was also an appreciable amount of methyl ester **55** formed in the reaction and the ratio of **16** : **55** (67 : 33) was determined by ^{1}H NMR analysis of the crude product.



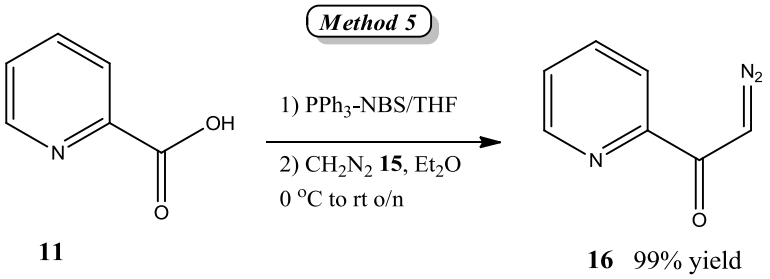
Scheme 2.18: Forbes' work to prepare α-diazoketone 16[53]

This approach was adopted in this work using diazoethane **20** in place of diazomethane **15** (**Scheme 2.19**) and the reverse order of addition was carried out (addition of reactive intermediate to diazoethane **20**) in comparison to Forbes' work.[53] The reverse order of addition was carried out in this project due to safety concerns regarding addition of potentially explosive diazoethane **20** to the intermediate. However, application of these conditions to 3-(pyridin-3-yl)propanoic acid **47** once again indicated no evidence for formation of the corresponding α-diazoketone **52** by ^{1}H NMR and infrared spectroscopy.



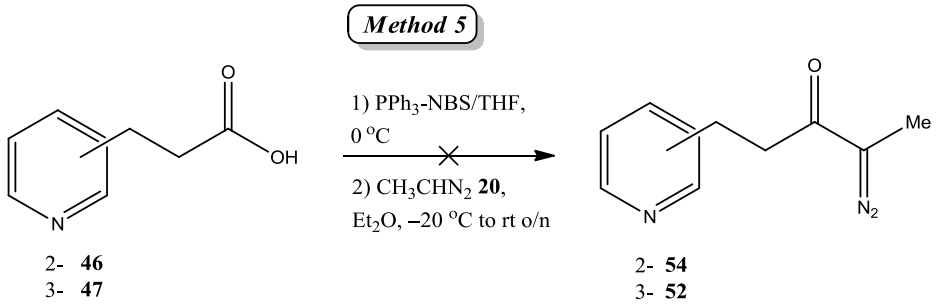
Scheme 2.19

Finally, a NBS/PPh_3-mediated coupling method published by Muchowski *et al*. was reported to be compatible with heterocyclic carboxylic acids such as furans, indoles and more importantly, picolinic acid **11**.[54] This method involved a tetrahydrofuran solution of triphenylphosphine and carboxylic acid **11** which was stirred at 0 °C followed by addition of tetrahydrofuran solution of NBS over 10 min to generate the acyloxyphosphonium salt. This salt was then reacted with ethereal diazomethane **15**, prepared from Diazald®, to generate the α-diazoketone **16** in an excellent 99% yield following purification by column chromatography (**Scheme 2.20**).



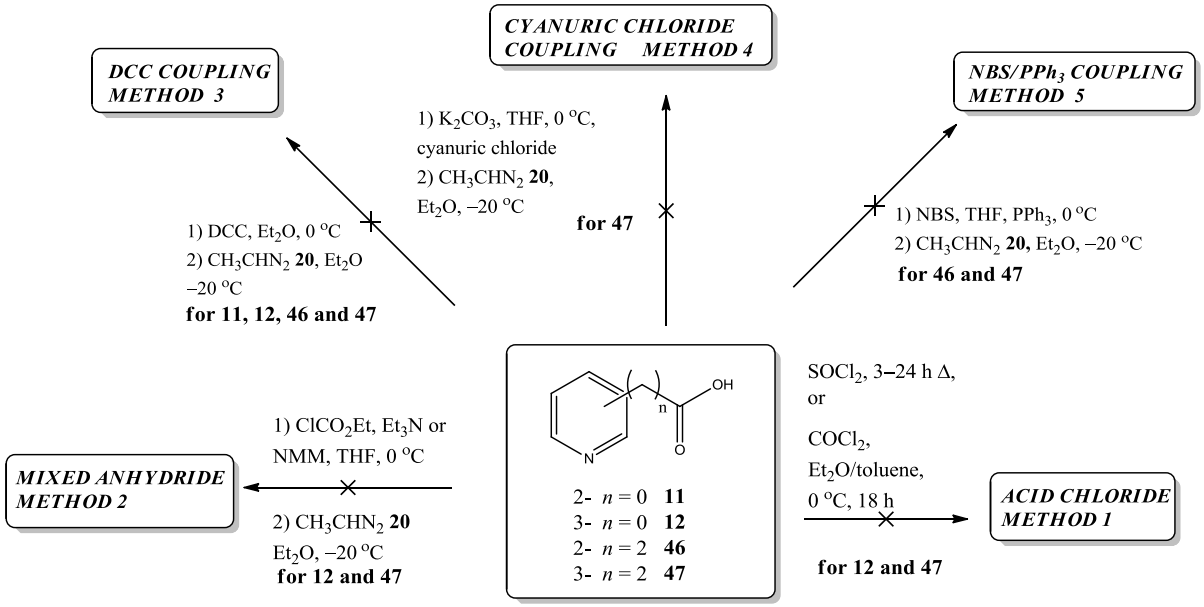
Scheme 2.20: Muchowski's work to prepare α-diazoketone 16[54]

Employing this procedure with acids **46** and **47** in this work, the α-diazoketones **52** and **54** were not generated in either case as determined by ^{1}H NMR and infrared spectroscopic analysis (**Scheme 2.21**). In this work, once again, the reverse order of addition was carried out due to safety concerns and diazoethane **20** was used in place of diazomethane **15**.



Scheme 2.21: NBS/PPh$_3$ and cyanuric chloride coupling

The overall summary of attempted acylation techniques is shown below (**Scheme 2.22**).



Scheme 2.22: Diazoethane acylation approaches attempted using pyridine substituted carboxylic acids

After the myriad unsuccessful acylation attempts, further investigation of the literature revealed an example of an isolated pyridine acid chloride, namely 2-chloronicotinoyl chloride **56**.[58] This, unlike many of the reported syntheses of pyridine acid chlorides was isolated, purified and characterised prior to further reactions. ^{1}H NMR and infrared spectroscopic data, as well as purification procedures *via* distillation were reported for this substrate.[58,59] It was also noticed that other halogenated pyridine acid chlorides could be purchased commercially, which suggested they are also reasonably stable.

The challenge in synthesising pyridine-containing acid chlorides is presumably associated with the intrinsic basicity of the pyridine ring and it can be rationalised that the introduction of appropriate groups adjacent to the pyridine nitrogen may be able to reduce this basicity. Katritzky has carried out thorough investigations into the properties of pyridine and substituted pyridine derivatives.[60] In that work, it was stated that electron-withdrawing groups (EWGs) decrease the N-atom reactivity towards electrophiles and conversely, electron-donating groups (EDGs) increase the N-atom reactivity towards electrophiles (**Figure 2.3**)

In comparison to the parent unsubstituted pyridine, it has been shown that the presence of extra N-atoms in the ring system considerably reduces the basicity of the pyridine lone pair through an inductive effect. An even more important factor is that substituents, particularly at the 2-position of the pyridine ring have a profound influence on the nitrogen nucelophilicity, with a range of EWGs and EDGs investigated (**Table 2.1**).

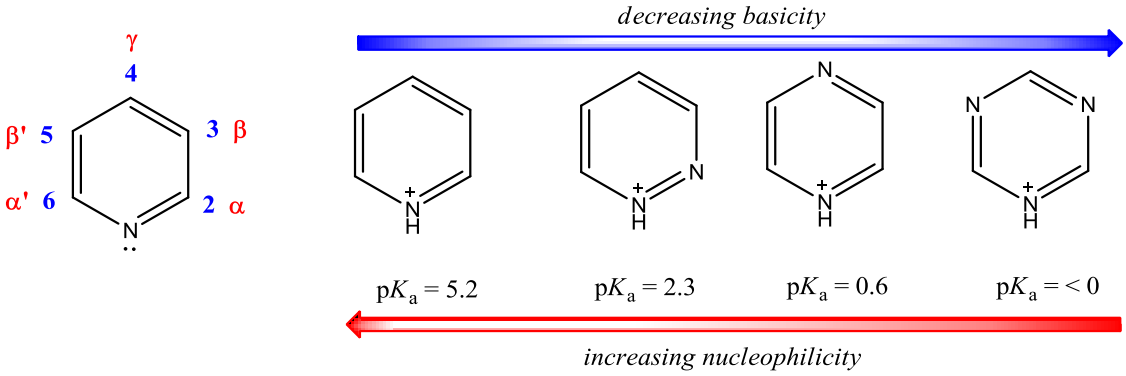


Figure 2.3

Table 2.1 *Effect of substituents on p*K_a *of Pyridinium ion (p*K_a *= 5.2)*[60]

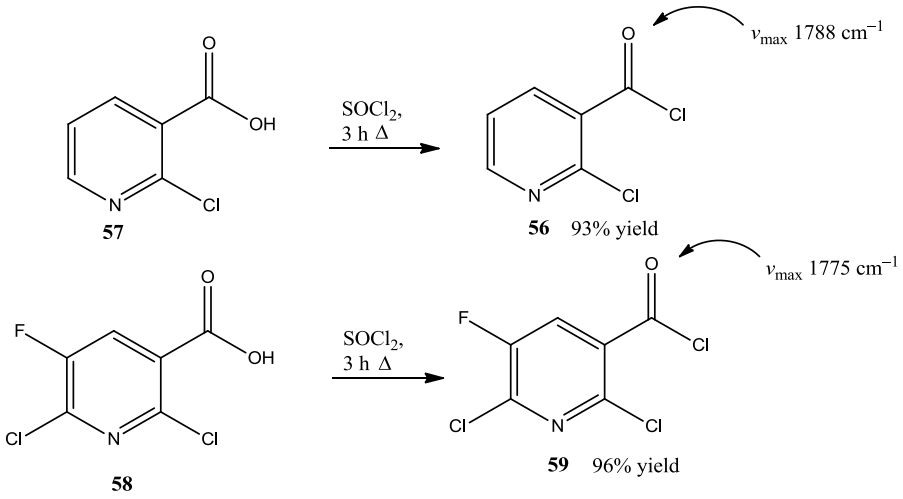
Position on ring	Me	NH_2	OMe	SMe	Cl	CN	NO_2	$CH(OH)_2$
2-position	+0.8	+1.7	–1.9	–1.6	–4.5	–5.5	–7.8	–1.4
3-position	+0.5	+0.9	–0.3	–0.7	–2.4	–3.8	–4.4	–1.4
4-position	+0.8	+4.0	+1.4	+0.8	–1.4	–3.3	–3.6	–0.5

Note: + sign indicates more basic than pyridine and – sign indicates less basic than pyridine.

In 1932, Graf postulated that formation of pyridine acid chlorides necessitates the presence of α-substituted electron-withdrawing groups to decrease the basicity of the ring nitrogen, thereby preventing formation of quaternary pyridinium salts.[61] This proof of concept was extended by Graf with the successful preparation of halogenated pyridine acid chloride derivatives.[62]

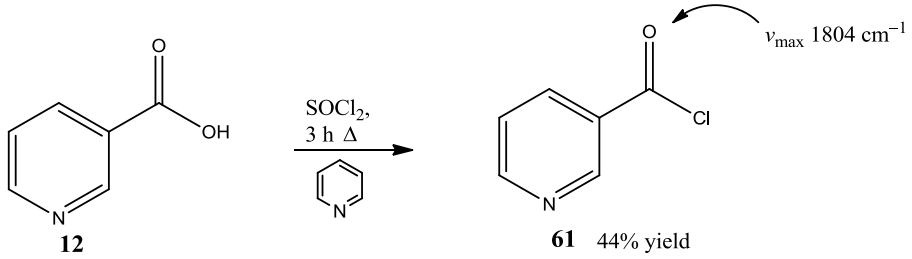
Based on this literature precedent, two commercially available halogenated pyridine carboxylic acids **57** and **58** were transformed to the corresponding acid chlorides **56** and **59** using thionyl chloride (**Scheme 2.23**),[63] while 6-chloronicotinoyl chloride **60** was commercially available. The reaction mixture was heated under reflux for 3 h followed by removal of the solvent *in vacuo*. The acid chlorides **56** and **59** were generated in high yields in

both cases with the characteristic stretch identified in the infrared spectrum (ν_{max} 1788 and 1775 cm^{-1}). For the preparation of 2-chloronicotinoyl chloride **56**, this was purified by vacuum distillation (b.p. 62 °C at 0.1 mmHg *cf.* lit.,[59] b.p. 98–100 °C at 2 mmHg) and this compound was isolated as a crystalline sweet-smelling solid. For 2,6-dichloro-5-fluoronicotinoyl chloride **59**, this was also purified by vacuum distillation (b.p. 52–55 °C at 0.1 mmHg *cf.* lit.,[64] b.p. 108–110 °C at 4 mmHg).



Scheme 2.23

Having achieved formation of pyridine acid chlorides above, formation of acid chloride from nicotinic acid **12** was attempted again, but this time in the presence of pyridine using the procedure outlined by Queguiner (**Scheme 2.24**).[32] Using this procedure, non-halogenated pyridine acid chloride **61** was synthesised in 44% yield after vacuum distillation (b.p. 45 °C at 0.1 mmHg *cf.* lit.,[32] b.p. 90 °C at 12 mmHg). After distillation, acid chloride **61** was found to contain ~46 mol% by ^{1}H NMR of an unknown impurity but the sample was brought forward without any further purification. The addition of an excess of pyridine to the crude mixture prior to vacuum distillation was the vital step in this process, presumably serving to scavenge any excess hydrochloric acid. In retrospect, addition of pyridine to the unsuccessful earlier attempts at acid chloride formation (**Scheme 2.15**) may have proved fruitful.



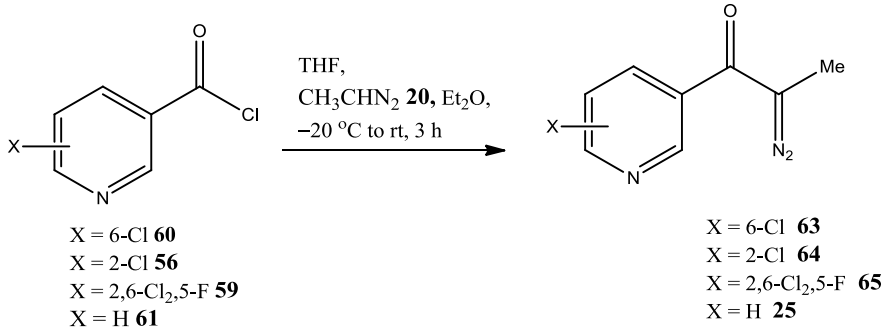
Scheme 2.24

Despite the earlier challenges in synthesising acid chlorides bearing pyridine rings, acid chlorides **56**, **59** and **61** were readily synthesised in multigram quantities, handled without

difficulty and stored without degradation. The next step involved reaction of the acid chlorides **56**, **59-61** with diazoethane **20** to generate the unsymmetrical α-diazoketones.

The main focus of this synthesis was to demonstrate that halogenated pyridine acid chlorides could provide α-diazoketones in the same way as their benzene counterparts. The standard procedure used in the Maguire research group involves formation of ethereal diazoethane **20** (typically ~7 equiv.) by basic decomposition of *N*-ethyl-*N*-nitrosourea **62** at –20 °C,[65] followed by dropwise addition of an ethereal solution of the acid chloride over 1 h at –20 °C.[8-12,17] In this work, tetrahydrofuran was used in place of ether as the pyridine acid chlorides were more soluble in this solvent.

Formation of all four α-diazoketones **25**, **63-65** was achieved (**Scheme 2.25**) with the characteristic diazo and carbonyl stretches identified in the infrared spectra of the compounds (**Table 2.2**). The α-diazoketones **25**, **63-65** were isolated as bright yellow oils after column chromatography which proved relatively stable and could be stored in a freezer for ~2 months without noticeable degradation. Purification of these compounds proved difficult, with clean samples only obtained after repeated chromatography in some cases, resulting in lower yields than typically observed. While α-diazoketones **63-65** are novel compounds, preparation of **25** has previously been described by Pitters and co-workers.[31] Each of the compounds was fully characterised during this work and the spectral characteristics of **25** were consistent with previously reported data.[31]



Scheme 2.25

Table 2.2 *Isolated yields and characteristic infrared and ^{1}H NMR spectroscopic signals for* ***25, 63-65***

Entry	Acid chloride	Diazo	Yield (%)[a]	ν_{CO}/cm^{-1}	ν_{CNN}/cm^{-1}	δ_H $CN_2C\underline{H}_3$[b] major rotamer	δ_H $CN_2C\underline{H}_3$[b] minor rotamer
1	**60**	**63**	45	1604	2077	2.17 ppm	–
2	**56**	**64**	28	1607	2082	2.16 ppm	2.01 ppm
3	**59**	**65**	21	1617	2081	2.14 ppm	2.02 ppm
4	**61**	**25**[31]	13	1605	2078	2.18 ppm	2.14 ppm

[a] Isolated yield after flash chromatography and in some cases, multiple attempts at purification by chromatography were required.

[b] ^{1}H NMR in $CDCl_3$ [(400 MHz for **63** and **65**) and (300 MHz for **25** and **64**)].

Proton NMR spectroscopy shows the signal for the methyl group adjacent to the diazo moiety (δ_H ~2.14–2.18 ppm) is located further downfield than the corresponding signal in the phenyl substituted α-diazocarbonyl compounds (δ_H ~1.70–1.90 ppm) previously synthesised in the research group (**Scheme 2.1**).[2,7,10,11] In both cases, the signal for the methyl group is observed as a broad signal in both the ^{1}H and ^{13}C NMR spectra, indicating restricted rotation due to extended conjugation (**Figure 2.4**). A weak and broad signal was observed for $\underline{C}N_2$ in the ^{13}C NMR spectra of α-diazoketones **25**, **63-65** in the region of δ_C ~63-67 ppm. Further analysis of **65** using ^{19}F NMR spectroscopy highlighted a singlet at δ_F 41.6 ppm in proton decoupled mode. In the ^{13}C NMR spectrum, spin-spin coupling by the fluorine atom results in the appearance of doublets for carbon atoms neighbouring the fluorine nucleus, with up to $^{4}J_{CF}$ coupling observed and expected values obtained (**Figure 2.4**). Interestingly, the coupling value for $\underline{C}$(3'), ($^{3}J_{CF}$ 1.7 Hz), was observed to be smaller than for the long-range coupling of $\underline{C}$(2')Cl, ($^{4}J_{CF}$ 2.2 Hz). This is consistent with data for monofluorinated pyridine systems described in the literature where coupling constants (J_{CF} values) are higher to $\underline{C}$(6) adjacent to the nitrogen.[66,67]

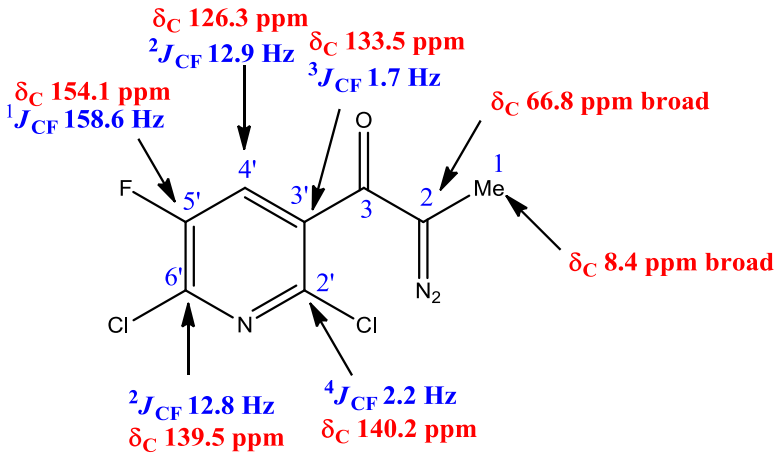


Figure 2.4: ^{13}C NMR values (125.8 MHz, $CDCl_3$) and carbon-fluorine coupling values of 65

The α-diazoketones **63-65** were further characterised by high resolution mass spectrometry. The molecular ion including nitrogen was identified in the nominal mass spectrum for **63** and **64**, but not in the case of **65**. In the high resolution mass spectrometry, the peaks characterised were the components with loss of nitrogen, which is a common, though not always observed phenomenon in high resolution mass spectrometry of α-diazocarbonyl compounds. In the case of the monochlorinated α-diazoketones **63** and **64**, the characteristic 3 : 1 chlorine isotope pattern was seen at $C_8H_7{}^{37}ClNO$ $[(M+H)–N_2]^+$, 170.0194 and $C_8H_7{}^{35}ClNO$ $[(M+H)–N_2]^+$, 168.0216. For the dichlorinated compound **65**, evidence for the isotopic pattern was also evident in the nominal mass spectrum, 221.9 {$[(C_8H_5{}^{37}Cl{}^{35}ClFN_3O–N_2)^+]$, 75%} and 219.9 {$[(C_8H_5{}^{35}Cl_2FN_3O–N_2)^+]$, 100%}, as well as identification in the high resolution mass spectrum $C_8H_5{}^{35}Cl_2FNO$ $[(M+H)–N_2]^+$, 219.9728.

The α-diazoketones were initially isolated as bright yellow oils which later solidified upon storage to provide bright yellow crystals. This enabled structural determination of α-diazoketones **63** and **65** by X-ray crystallography (**Figure 2.7** and **2.8**). Rotamers are defined as isomers which can be interconverted exclusively by rotations around a single bond.[68] Diazoketones can adopt two rotameric structures *syn* or *anti* and interestingly, the crystal structure of **65** showed the *anti*-orientation while that of **63** showed the *syn*-orientation. The observation of both rotamers in the solid state is consistent with the presence of rotamers in the ^{1}H NMR spectra. Thus, both rotamers exist in solution while in the solid state one is preferred for each compound due to packing differences. While ^{1}H NMR spectroscopy for **63** showed no evidence of rotamers, clear evidence of rotamers was seen in the ^{1}H NMR spectra of 2-chlorine substituted α-diazoketones **64** and **65** (**Figure 2.5**), rationalised due to restricted rotation in the presence of the 2-chlorine substituent. Interestingly, the minor rotamer accounted for ~10% of the material in the isolated samples of both **64** and **65**, which is highlighted in red below (**Figure 2.5**).

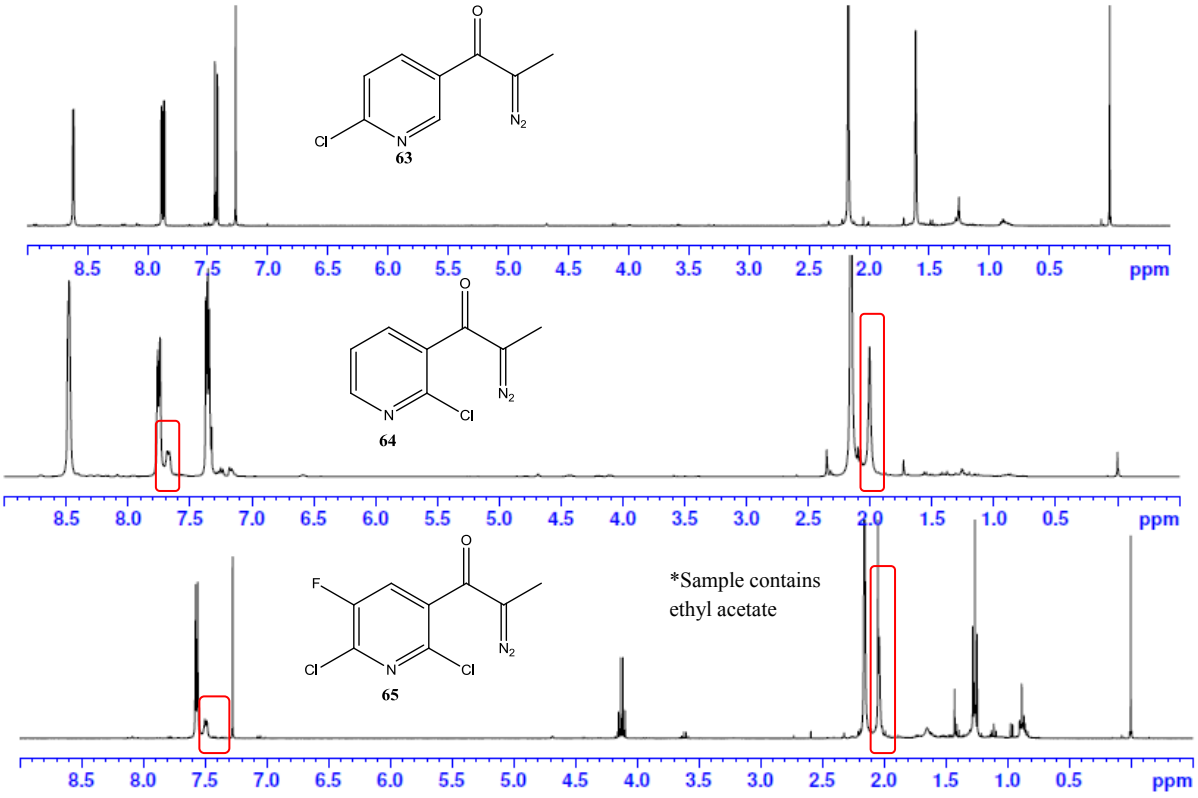


Figure 2.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectra of 63, 64 and 65 illustrating the existence of rotamers (ethyl acetate slightly overlaps with broad singlet for minor rotamer for 65)

Through comparison of theoretical studies and experimental infrared spectra, Wentrup and co-workers have identified the existence of rotamers for 2-substituted pyridine derivative **16**, resulting in an s-*cis* and s-*trans* orientation of the carbonyl and diazo groups (**Figure 2.6**).[69] Reaction of α-diazoketone **16** under photochemical or flash vacuum pyrolysis conditions

resulted in the generation of ketenes. In the present work, the adjacent carbonyl and diazo groups were observed in an s-*trans/anti* alignment for **65** and an s-*cis/syn* orientation for compound **63**, in the X-ray crystal structures obtained (**Figures 2.7** and **2.8**). The dihedral angle between the carbonyl and diazo groups in **63** is –9.37°, illustrating minor deviation from planarity due to packing constraints. Similarly, the corresponding dihedral angle between the carbonyl and diazo groups in the *anti*-oriented compound **65** is 173.5°. In the crystal structure of **65**, a Cl···O halogen bonding interaction is observed (~3.00 Å), while the crystal structure of **63** shows a weak hydrogen bond for the methyl C–H···O interaction (~2.39 Å).

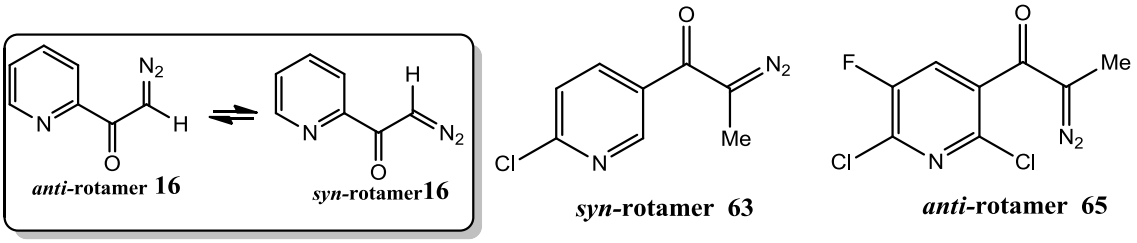


Figure 2.6: Rotamers observed by Wentrup[69] using infrared spectroscopy and those in this work as indicated using X-ray crystallography

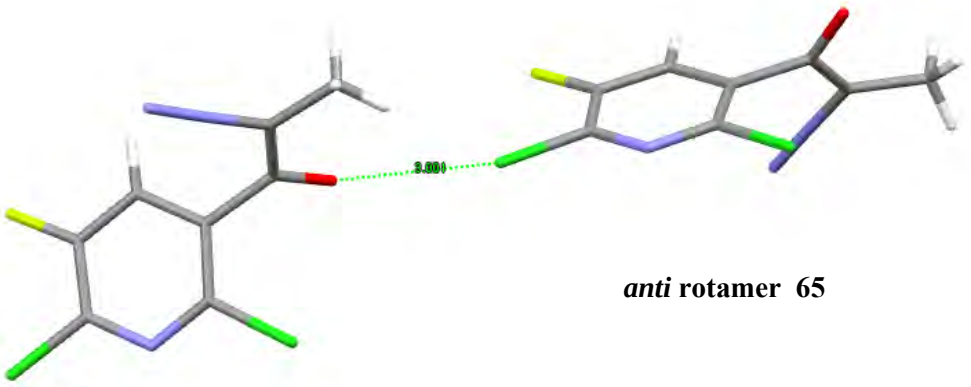


Figure 2.7: X-ray crystal structure of 65

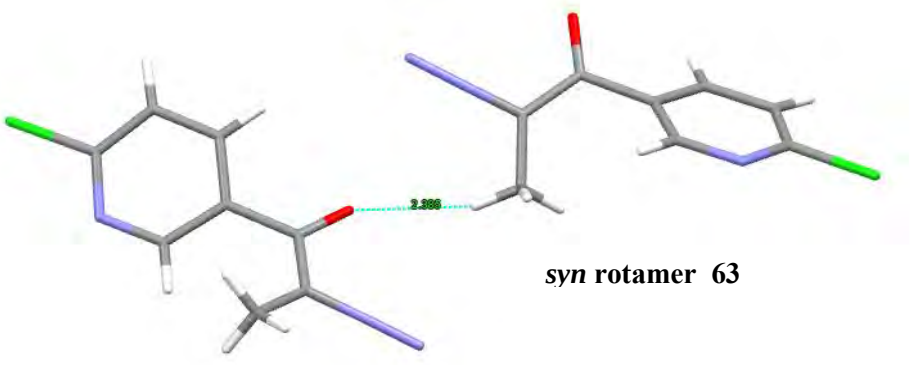


Figure 2.8: X-ray crystal structure of 63

The successful isolation of the α-diazoketones **25**, **63-65** illustrated that once the precursor acid chlorides could be obtained, transformation to the stable α-diazoketones is relatively straightforward. Use of halogenated pyridines as a strategy to provide stable acid chlorides has a clear advantage, although the successful synthesis of the unsubstituted derivatives **61** and **25**, which was achieved late in this work clearly indicates a synthetic route to pyridyl α-diazoketones without halogen substituents.

The synthesis of halogenated pyridine acid chlorides has been described in the literature in the context of overcoming the formation of acid chloride hydrochloride salts,[61,62] though it has received little attention.

2.3.1.3 Synthesis of substituted 3-pyridylpropanoic acids

As synthesis of pyridine α-diazoketones **63-65** *via* the corresponding acid chlorides was achieved through introduction of halogen substituents at C(2) or C(6) adjacent to the nitrogen atom in the pyridine ring, attention next focused on the synthesis of 3-pyridylpropanoic acids, again bearing halogen substituents adjacent to the nitrogen atom of the ring. A summary of the various substituents used in this project is shown below (**Figure 2.9**).

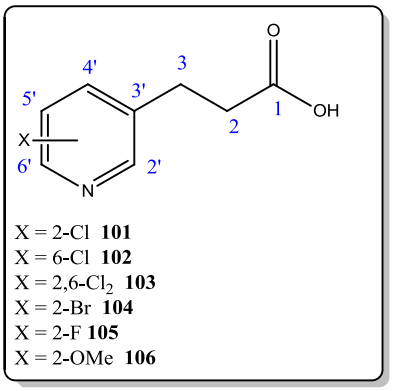
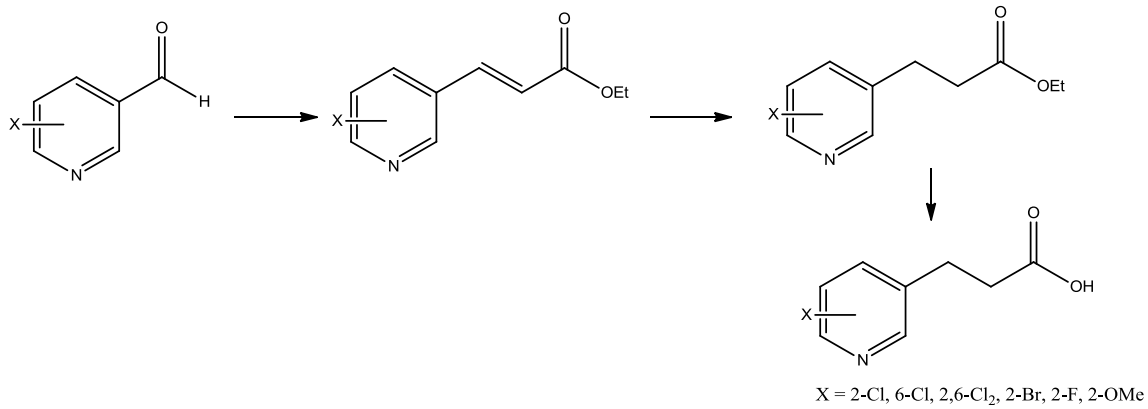


Figure 2.9

The carboxylic acids **101-106** were selected as precursors for the α-diazoketone synthesis. The synthetic strategy for the synthesis of the 3-pyridinepropanaoic acids is summarised in **Scheme 2.26**. Thus, the pyridinecarboxaldehydes were initially synthesised and then subjected to the Horner-Wadsworth-Emmons methodology to generate the α,β-unsaturated esters, followed by hydrogenation and hydrolysis to provide the 3-pyridinepropanoic acids.

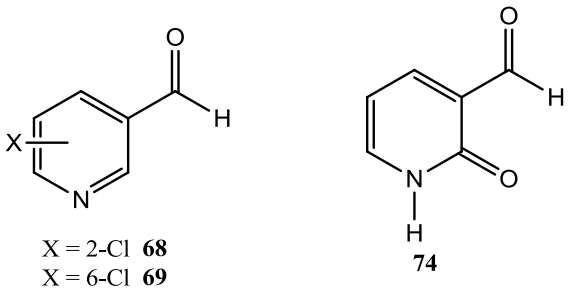
Long-chain derivatives



Scheme 2.26

2.3.1.3.1 Synthesis of substituted aldehydes

The pyridinecarboxaldehydes required for the synthesis of carboxylic acids **101-106** are summarised in **Figure 2.10**. In addition, the pyridonecarboxaldehyde **74** was also synthesised.



X = 2-Cl **68**
X = 6-Cl **69**
X = 2,6-Cl_2 **70**
X = 2-Br **71**
X = 2-F **72**
X = 2-MeO **73**

74

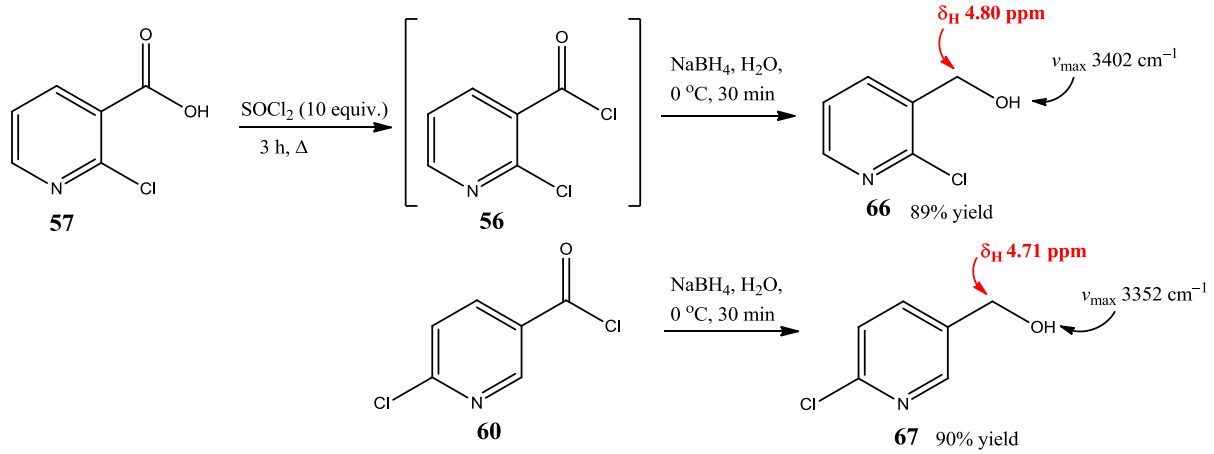
Figure 2.10

In the course of this work, two approaches were employed to provide these substituted pyridinecarboxaldehydes. Both procedures have been reported in the literature for substrates either identical or similar to substrates investigated in this work.[70-77] The two procedures were:

> Method 1: Reduction of an acid chloride followed by oxidation of the alcohol or,
>
> Method 2: Directed *ortho*-metalation (D*o*M) of substituted pyridines leading to H–metal exchange, followed by quenching of the aryllithium with an electrophile.

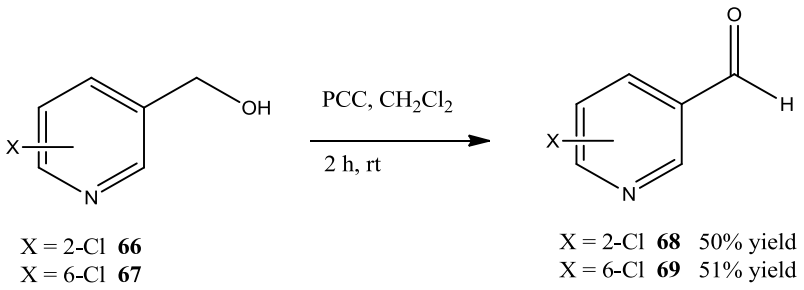
The preparation of 2-chloronicotinaldehyde **68** was undertaken as described previously by Metay,[70] with minor modifications, as outlined below. This procedure involves reduction of

an acid chloride using sodium borohydride ($NaBH_4$) to provide the alcohol, which is subsequently oxidised to the aldehyde. The acid chloride **56** was synthesised as described earlier (**Section 2.3.1.1**),[63] from 2-chloronicotinic acid **57** using thionyl chloride under reflux. Unlike the synthesis of **56** for α-diazoketone synthesis (**Scheme 2.23**), the acid chloride was not further purified in this instance and instead was brought forward crude for the reduction step following Metay's procedure. While Metay carried out portionwise addition of the solid acid chloride **56** to a solution of sodium borohydride in water,[70] initial attempts to undertake this resulted in a very vigorous reaction. Accordingly, a modified approach developed in this work involved dropwise addition of a tetrahydrofuran solution of acid chloride **56** over 15 min to the aqueous sodium borohydride mixture. The same modified procedure was followed for commercially available 6-chloronicotinoyl chloride **60**. The two alcohols were formed in excellent purity without requiring purification in 89% yield for **66** and 90% yield for **67** (**Scheme 2.27**). Confirmation of the reduction was indicated by ^{1}H NMR spectroscopy showing a singlet located at δ_H 4.71 or 4.80 ppm for **67** and **66** respectively, accounting for the methylene group. Infrared spectroscopy displayed the absence of an acid chloride peak and appearance of a broad O–H peak at ν_{max} 3402 and 3352 cm^{-1} for **66** and **67** respectively. The spectroscopic data for **66** were consistent with that described by Metay[70] while values for **67** were in accordance with those reported by Loh.[78]



Scheme 2.27

The next step involved oxidation of the alcohol to the corresponding aldehyde using pyridine chlorochromate (PCC), following a procedure described again by Metay.[70] Each of the alcohols **66** and **67** were transformed to pyridinecarboxaldehydes **68** and **69** and isolated as highly crystalline solids in modest yields following silica gel column chromatography (**Scheme 2.28**). The melting points obtained were in close agreement with the literature values, 48–50 °C *cf.* lit.,[72] 50 °C for **68** and 75–76 °C *cf.* lit.,[79] 70–71 °C for **69**. While the isolated yields of the pyridinecarboxaldehydes were lower than those obtained by Metay,[70] this route provided ready access to multigram quantities of **68** and **69** required for the subsequent step and therefore no attempt was made to optimise this synthesis.



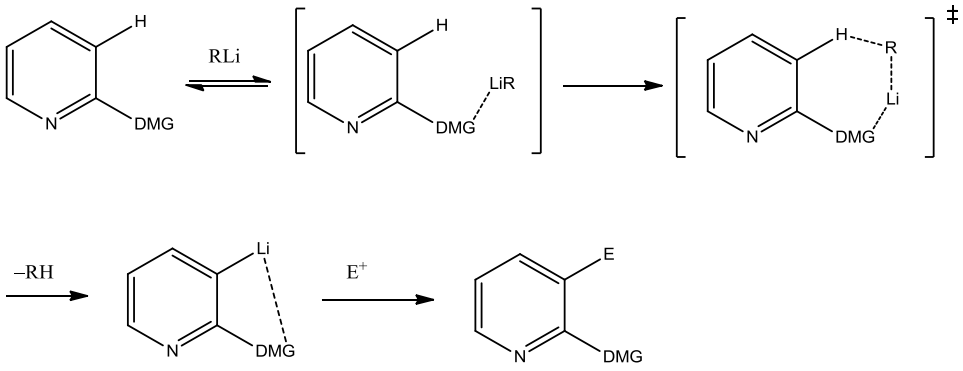
X = 2-Cl **66**
X = 6-Cl **67**

X = 2-Cl **68** 50% yield
X = 6-Cl **69** 51% yield

Scheme 2.28

Although the other required aldehydes **70-72** are commercially available, they are very costly and accordingly it was decided to synthesise substituted pyridinecarboxaldehydes **70-72** using established procedures to generate sufficient material for the subsequent steps.

The approach adopted for these compounds involved directed *ortho*-metalation (D*o*M) through the use of a directed metalation group (DMG), *i.e.* method 2 above, which favours deprotonation at the *ortho* position. Snieckus and co-workers spearheaded the development of this methodology through significant contributions throughout the 1980s.[80-86] The directed metalation groups favour *ortho*-metalation by an inductive effect (*e.g.* halogens) which lowers the pK_a of the adjacent proton or by stabilising the pyridyllithium through chelating effects (*e.g.* alkoxides or amides).[87] In the latter case, the stabilisation is known as a complex-induced proximity effect (CIPE), as originally described by Beak.[88] The CIPE involves a complex in which the alkyllithium is held in close proximity to the *ortho* position by the DMG, facilitating a slow but irreversible proton abstraction to form the coordinated *ortho*-lithiated species.[88-90] This is followed by quench with an electrophile to generate the regioselective product in the case when the DMG is situated at the 2-position on the ring, while substitution at the 3-position results in a mixture of 2- and 4-lithiated pyridines.[91] The general mechanism of directed *ortho*-metalation utilising the complex-induced proximity effect is shown below (**Scheme 2.29**), while specific examples of both types of DMGs involving a pyridine ring are illustrated in **Figure 2.11**.



Scheme 2.29: Illustration of complex-induced proximity effect (adapted from Beak[88,90])

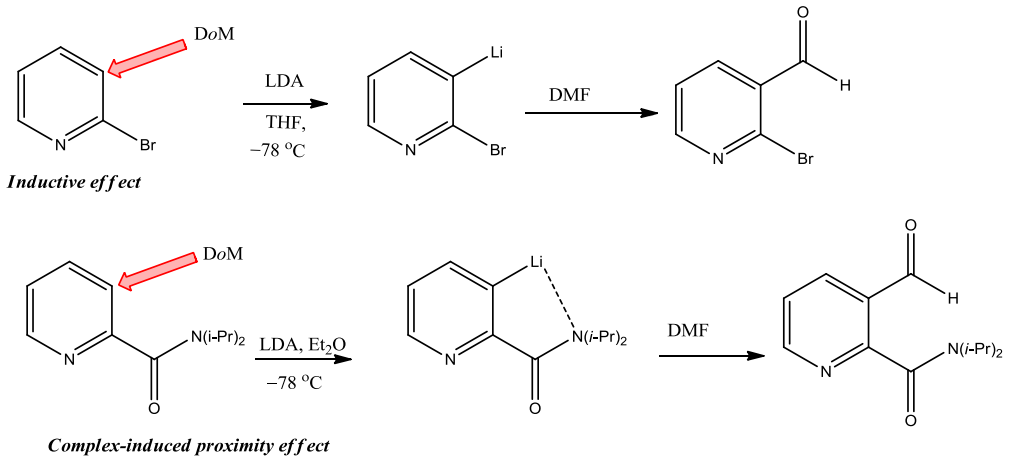
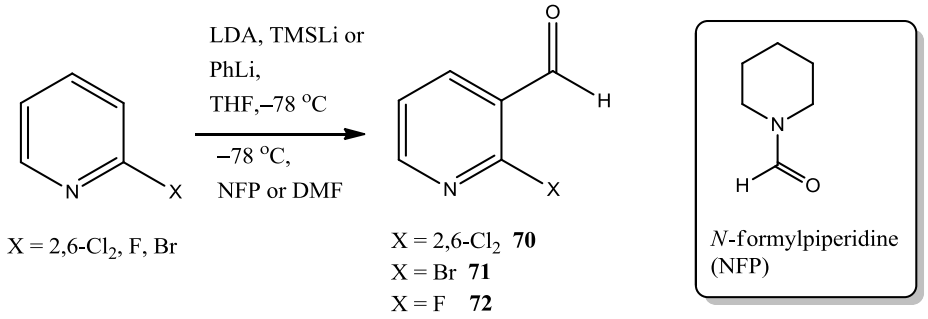


Figure 2.11: Directed *ortho*-metalation involving inductive[92] and complex-induced proximity effect[93] in pyridine rings

The regioselective metalation of halogentated pyridines has been extensively investigated by Queguiner,[72,91,94-97] Bracher[73] and Radinov.[71] The 2-halogenated pyridines were lithiated with a strong base such as lithium diisopropylamide (LDA), trimethylsilyllithium (TMSLi) or phenyllithium (PhLi) and quenched by reaction with *N*-formylpiperidine (NFP) or *N*,*N*-dimethylformamide (DMF) (**Scheme 2.30**). The reactions were generally carried out at low temperatures, –40 °C to –80 °C, with a slight excess (1.1 equiv.) of the base. In this work, the pyridinecarboxaldehydes **70-72** were synthesised using NFP and LDA as summarised in **Table 2.4**, leading to each of the products as white crystalline solids in modest yields. In general, the spectroscopic characteristics were consistent with the literature data except for a slight difference in the carbonyl band of **71**.



Scheme 2.30

The first of these substrates investigated in this work was 2,6-dichloropyridine, which has been utilised by Radinov to prepare 2,6-dichloronicotinaldehyde **70** and the reaction conditions involved LDA (1.0 equiv.) as base and NFP (1.0 equiv.) as the electrophile (**Table 2.3**, entry 1).[71] In that work, pyridinecarboxaldehyde **70** was formed in 60% yield and the reaction mixture also contained a small amount of the 4-substituted regioisomer. Mallet also described the formation of **70** in 55% yield using PhLi and NFP (**Table 2.3**, entry 2).[77] In 2006, Leonard and co-workers reported the synthesis of aldehyde **70** using LDA and DMF. However, no yield or detailed experimental procedure was provided for this synthesis.[98]

In the present investigation, following Radinov's conditions using equimolar quantities of NFP, LDA and 2,6-dichloropyridine,[71] 2,6-dichloronicotinaldehyde **70** was successfully isolated as a white solid in 49% yield (**Table 2.4**, entry 1) and structural confirmation was determined by ^{1}H NMR and infrared spectroscopic analysis. Spectroscopic properties obtained for **70** were consistent with previously reported data,[71,77] while the melting point of the white solid was in good agreement with the reported literature value, 72–75 °C *cf.* lit.,[99] 74–74.5 °C.

Bracher and co-workers have prepared 2-bromonicotinaldehyde **71** from 2-bromopyridine in 51% yield using LDA (1.13 equiv.) followed by DMF (3.05 equiv), (**Table 2.3**, entry 3),[92] while more recently, Spivey reported a 72% yield employing similar conditions (**Table 2.3**, entry 4),[74] although using more equivalents of the base (1.30 equiv.[74] *cf.* 1.13 equiv.[92]) and electrophile (8.7 equiv.[74] *cf.* 3.05 equiv.[92]).

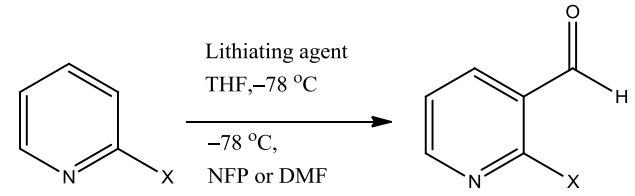
In our investigations, using a modification of Bracher's procedure,[92] replacing DMF with NFP (3.0 equiv.) and using LDA (1.1 equiv.), the pyridinecarboxaldehyde **71** was prepared as a crystalline white solid in 40% yield (**Table 2.4**, entry 2). While the ^{1}H NMR characteristics were in agreement with those described by Bracher[92] and Spivey,[74] the carbonyl stretch in the infrared spectrum was slightly altered at ν_{max} 1702 cm^{-1}.

The last substrate explored using this strategy was 2-fluoropyridine and efficient preparation of 2-fluoronicotinaldehyde **72** was disclosed by Mallet (**Table 2.3**, entries 7 and 8),[72,77] and in two patents by FMC Corporation (**Table 2.3**, entry 5)[75] and INCYTE Corporation respectively (**Table 2.3**, entry 6).[76] As was the case for the metalation of 2,6-dichloropyridine, Mallet used PhLi as the base and NFP as the electrophile with the regioselective aldehyde **72** formed in 60% yield.[77] In the INCYTE patent,[76] a 45% yield was reported when LDA (1.09 equiv.) was used as the base and DMF (2.01 equiv.) used as the electrophile. However, on using TMSLi (7.38 equiv.), FMC Corporation achieved formation of the aldehyde **72** in an excellent 90% yield employing NFP (1.03 equiv.) as the electrophile in this case.[75]

In this work, the fluoro substituted aldehyde **72** was generated in 49% yield using LDA as base (1.1 equiv.) and NFP (1.0 equiv.) as the electrophile (**Table 2.4**, entry 3). Analysis of **72** was carried out using ^{1}H NMR and infrared spectroscopy. ^{1}H NMR spectroscopic data was consistent with values described in the literature.[76,77]

A comparison of the yields reported in the literature (**Table 2.3**) and those obtained in this work (**Table 2.4**) is shown below.

Table 2.3 *Literature syntheses to provide pyridinecarboxaldehydes*



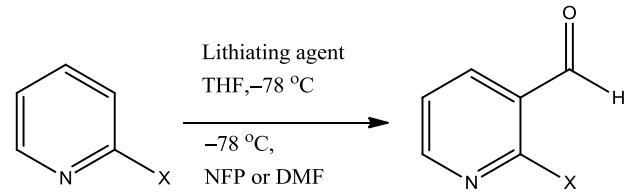
X = 2,6-Cl_2, F, Br

X = 2,6-Cl_2 **70**
X = Br **71**
X = F **72**

Entry	Aldehyde	Electrophile (equiv.)	Lithiating agent (equiv.)	ν_{max}/cm^{-1}	Yield (%)[a]
1	2,6-Cl_2 **70**	NFP (1.0)	LDA (1.0)	1685	60[71]
2	2,6-Cl_2 **70**	NFP (3.3)	PhLi (3.4)	1690	55[77]
3	2-Br **71**	DMF (3.05)	LDA (1.13)	1690	51[92]
4	2-Br **71**	DMF (8.7)	LDA (1.30)	1690	72[74]
5	2-F **72**	NFP (1.03)	TMsLi (7.38)	–	90[75]
6	2-F **72**	DMF (2.01)	LDA (1.09)	–	45[76]
7	2-F **72**	DMF (2.7)	PhLi (3.4)	1700	50[72]
8	2-F **72**	NFP (3.3)	PhLi (3.4)	1700	60[77]

[a] Isolated yield after column chromatography.

Table 2.4 Ortho-*lithiation to provide pyridinecarboxaldehydes*



X = 2,6-Cl_2, F, Br

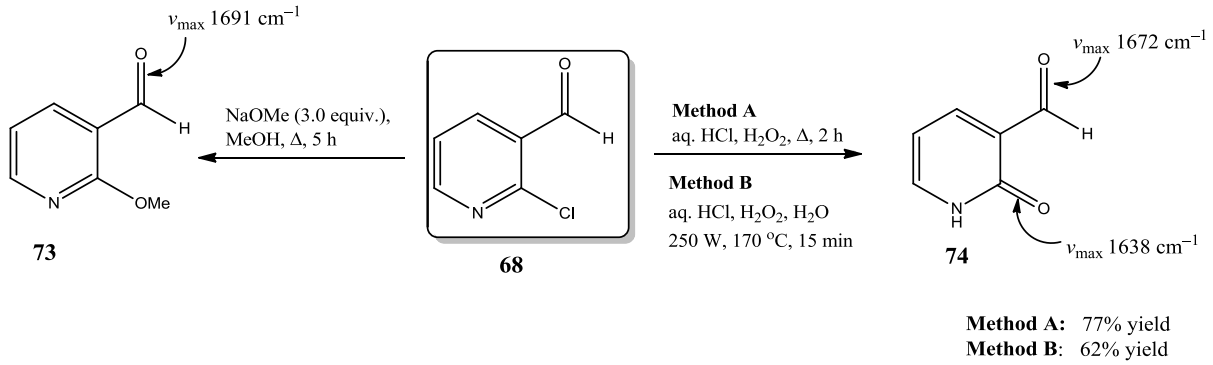
X = 2,6-Cl_2 **70**
X = Br **71**
X = F **72**

Entry	Aldehyde	Electrophile (equiv.)	Lithiating agent (equiv.)	ν_{max}/cm^{-1}	Yield (%)[a]
1	2,6-Cl_2 **70**	NFP (1.0)	LDA (1.0)	1686	49
2	2-Br **71**	NFP (3.0)	LDA (1.1)	1702	40
3	2-F **72**	NFP (1.0)	LDA (1.1)	1705	49

[a] Isolated yield after column chromatography.

While the yields of pyridinecarboxaldehydes obtained in this work were usually lower than described in the literature, as enough material was synthesised for use in subsequent Horner-Wadsworth-Emmons procedures, these processes were not optimised in the course of this project.

Queguiner has demonstrated that further functionalisation of pyridinecarboxaldehydes can be carried out using 2-chloronicotinaldehyde **68**.[96] Employing this strategy in this work, 2-methoxynicotinaldehyde **73** and the pyridone tautomer of 2-hydroxynicotinaldehyde **74** were generated in one-step from 2-chloronicotinaldehyde **68** (**Scheme 2.31**).



Scheme 2.31: Functionalisation of 68 to prepare 73 and 74

The formation of 2-methoxynicotinaldehyde **73** from **68** and sodium methoxide in methanol afforded carboxaldehyde **73** as a bright yellow oil, which was sufficiently pure to use without further purification. ^{1}H NMR spectroscopic properties were consistent with reported values by Queguiner,[96] while in the infrared spectrum, the carbonyl band slightly deviated at ν_{max} 1691 cm^{-1} (lit.,[96] ν_{max} 1680 cm^{-1}). However, the carbonyl stretching frequency in this work was in agreement with subsequent syntheses of **73** reported by Mallet[77] and Struk.[100]

In the preparation of 2-pyridonecarboxaldehyde **74**, two approaches were utilised in this work, a thermal procedure outlined by Queguiner[96] and microwave irradiation employed by Saubern.[101] In contrast to the methoxy substituent, replacement of the chloride by hydroxide leads to the isolation of the more stable pyridone tautomer as evidenced by infrared spectroscopy (ν_{max} 1675 and 1640 cm^{-1}).[96]

Conditions for the thermal protocol involved heating with aqueous hydrochloric acid and 30% hydrogen peroxide (4 drops) under reflux for 2 h (**Scheme 2.31**). After neutralisation using aqueous K_2CO_3, yellow solid was collected by filtration in 77% yield (lit.,[96] 80% yield). A melting point of 220 °C (lit.,[96] 224 °C) was obtained. Analysis by infrared spectroscopy as discussed by Queguiner indicated that aldehyde **74** has a pyridone structure,[96] possessing two carbonyl signature frequencies which were observed at ν_{max} 1672 and 1638 cm^{-1}, with the latter stretch characteristic of a pyridone ring.

Employing Saubern's procedure on a slightly reduced scale, the reaction mixture was stirred and heated for 15 min at 250 W at 170 °C, followed by evaporation under reduced pressure to give the crude 2-oxo-1,2-dihydropyridine-3-carboxaldehyde **74** in 62% yield (**Scheme 2.32**). The microwave method allowed formation of **74** in a shorter time than the thermal reaction (0.25 h *cf.* 2 h) while also using considerably less acid than the thermal reaction, eliminating use of neutralisation in the work up. Further noteworthy attributes of microwave irradiation

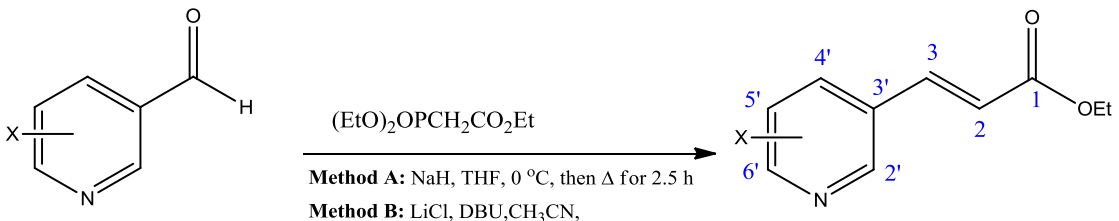
include cleaner reactions, less side products generated and milder reaction conditions compared to conventional thermal procedures.[102]

In Queguiner's work,[96] signals in the ^{1}H NMR spectrum of **74** at δ_H 7.83 ppm (dd, *J* 6.5 and 2.5 Hz) and δ_H 8.00 ppm (dd, *J* 7.0, 2.5 Hz) were attributed to C(6)H and C(4)H respectively. These values were in general agreement with chemical shifts of protons associated with a pyridone ring,[103] while Saubern did not assign the pyridone protons (δ_H 7.80 and 7.96 ppm) in his work.[101] In our work using the microwave procedure, ^{1}H NMR signals were seen at δ_H 7.81 and 7.98 ppm, with similar *J* values of 6.0, 2.0 Hz and 6.8, 2.0 Hz observed. However, definitive assignment of C(4)H and C(6)H was not made in this project due to the similarity of the coupling constants.

In conclusion, multigram quantities of each of the pyridinecarboxaldehydes were prepared following the literature procedures for use in the subsequent synthetic steps.

2.3.1.3.2 Formation of unsaturated and saturated esters

Preparation of each of the α,β-unsaturated esters **75-80** was achieved by Horner-Wadsworth-Emmons reaction with the pyridinecarboxaldehydes **68-73** (**Scheme 2.32**). Two methods were explored for this condensation; sodium hydride in THF as described by Kato (Method A)[41] and secondly, LiCl and DBU as employed by Bouziane (Method B).[35] In this work, Method A was explored for each of the aldehydes **68-73** while Method B was used for aldehydes **68**, **71** and **73**.



X = 2-Cl **68**
X = 6-Cl **69**
X = 2,6-Cl_2 **70**
X = 2-Br **71**
X = 2-F **72**
X = 2-OMe **73**

X = 2-Cl **75**
X = 6-Cl **76**
X = 2,6-Cl_2 **77**
X = 2-Br **78**
X = 2-F **79**
X = 2-OMe **80**

Scheme 2.32

Table 2.5 *Synthesis of α,β-unsaturated esters* via *Horner-Wadsworth-Emmons reaction using Methods A and B*

Entry	Aldehyde	Ester	Yield (%)[a]	
			Method A	Method B
1	2-Cl **68**	**75**[41,70]	98	56
2	6-Cl **69**	**76**[104,105]	56	–
3	2,6-Cl_2 **70**	**77**	37	–
4	2-Br **71**	**78**	34	73
5	2-F **72**	**79**	50	49
6	2-MeO **73**	**80**	54	–

[a] Isolated yield after column chromatography.

Kato and co-workers previously prepared (*E*)-ethyl 3-(2-chloropyridin-3-yl)acrylate **75** from 2-chloronicotinaldehyde **68**.[41] This procedure was applied in this work to prepare **75** with one modification. Following complete addition of aldehyde **68** to the phosphonate-stabilised carbanion at 0 °C, a sticky brown residue was observed at the bottom of the round-bottomed flask, which prevented the reaction mixture from stirring. This phenomenon was also found for compounds **69-73** and this issue was rectified by heating the reaction mixture under reflux for 2.5 h, although Kato had not reported this.[41] The product was isolated by workup as described by Kato.[41] Purification by column chromatography provided the α,β-unsaturated ester **75** in high yield. Method A was similarly employed with aldehyde substrates **69-73**, while in addition, Method B was employed for 2-chloro-, 2-bromo- and 2-fluoronicotinaldehyde **68**, **71** and **72** (**Table 2.5**). From the results obtained above (**Table 2.5**), there is no particular advantage in use of Method A or Method B for the reaction.

Structural identity for previously described compounds **75**[41,70] and **76**[104,105] was aided by ^{1}H NMR and infrared spectroscopic analysis and was consistent with the reported data. The novel esters **77-80** were further characterised by melting point, ^{13}C NMR spectroscopy, and both nominal and high resolution mass spectrometry. An interesting observation from the ^{1}H NMR spectrum of esters **75-80** was that one of the alkene signals, C(3)H, overlapped with the C(5')H signal of the pyridine ring using $CDCl_3$ as solvent, but using DMSO-d_6 as solvent the alkene signal was distinct. It has been ascertained that protons in the α-position [C(2')H or C(6')H] to the ring nitrogen are more deshielded and have smaller coupling constants than protons in the γ-position [C(4')H],[103] which can help distinguish between signals for C(6')H and C(4')H possessing similar chemical shifts. In the ^{13}C NMR spectrum of methoxy substituted ester **76**, assignment of the C(5')H (δ_C 116.9 ppm) was aided by comparison with actual (δ_C 116.7 ppm)[106] and predicted (116.6 ppm)[107] values for related 2-methoxypyridine. While the C(5')H signal normally appears in the region δ_C ~120–128 ppm in the ^{13}C NMR spectra of monosubstituted pyridines, the strong shielding effect of the methoxy group accounts for the altered chemical shift. It is noteworthy that carbons located in the *para* position to the substituent (*e.g.* positions 2- and 5-) of monosubstituted pyridines exhibit a strong shielding effect, resulting in lower than expected chemical shifts. This is particularly evidenced in the case of alkoxy and amine substituents.[108] Assignment of signals was

relatively straightforward for all but one of the α,β-unsaturated esters, with the fluorine-substituted unsaturated ester **79** proving more difficult to assign.

Analysis of monosubstituted esters **75**, **76**, **78** and **80** by ^{1}H NMR spectroscopy illustrates the sequence of the protons for the pyridine ring correlates very well across the range of substrates. This sequence shows the signal for C(5')H located furthest upfield, followed by C(4')H and the signal for C(2')H or C(6')H located furthest downfield. This is highlighted below (**Figure 2.12**).

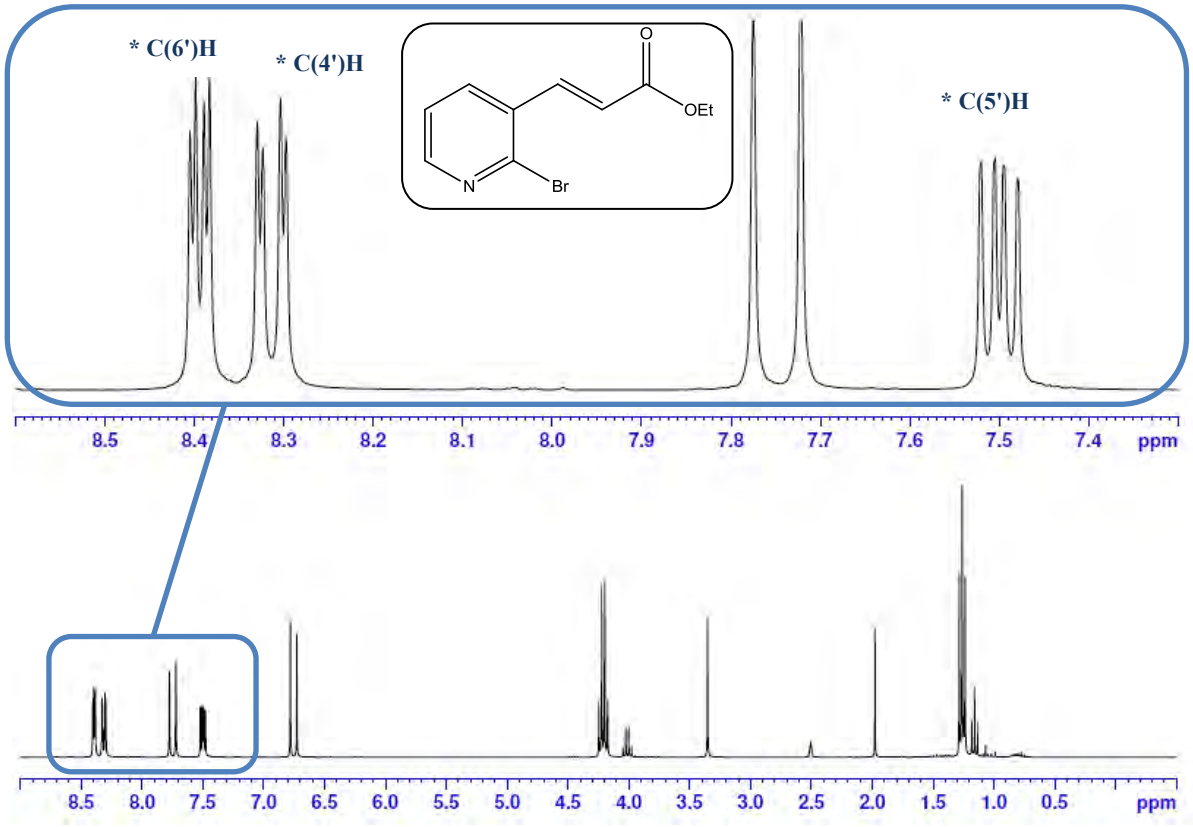


Figure 2.12: ^{1}H NMR spectrum and expansion (400 MHz, DMSO-d_6) of ester 78

The fluorine-substituted ester **79**, as expected, exhibits extra splitting patterns in the ^{1}H NMR (**Figure 2.13**) and ^{13}C NMR (**Figure 2.14**) spectra. Proton NMR analysis shows the hydrogens on the pyridine ring displayed extra splitting, with three doublets of doublets of doublets observed at δ_H 7.45 (*J* 7.5, 4.8, 1.8 Hz), 8.29 (*J* 4.8, 1.8, 1.2 Hz) and 8.45 (*J* 9.6, 7.5, 1.8 Hz) ppm for C(5')H, C(6')H and C(4')H respectively using DMSO-d_6 as solvent. The presence of this splitting pattern indicates that HF spin coupling is observed. The sequence of the pyridine protons varied slightly for the (*E*)-ethyl 3-(2-fluoropyridin-3-yl)acrylate **79** with the order from upfield to downfield: C(5')H, C(6')H and C(4')H.

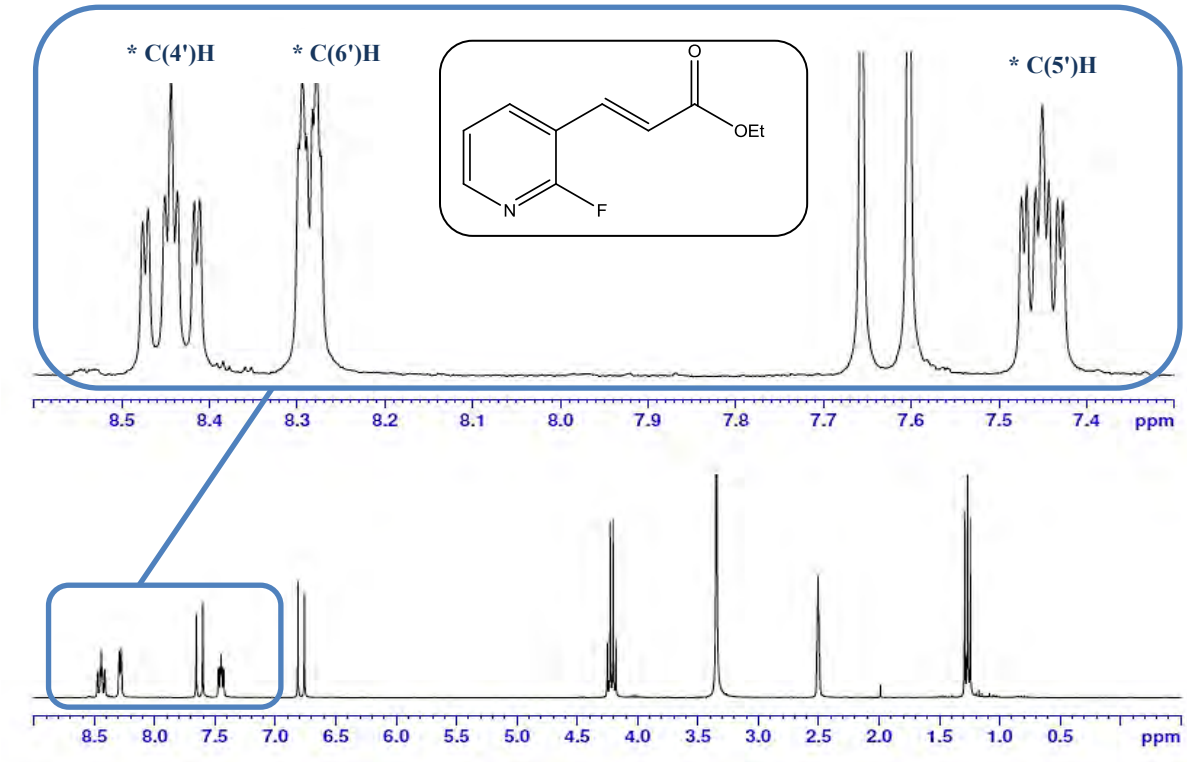


Figure 2.13: ^{1}H NMR spectrum and expansion (300 MHz, DMSO-d_6) of ester 79

A ^{1}H–^{13}C HETCOR experiment helped elucidate the assignment of C(4')H and C(6')H as the corresponding signals show up at different positions in the ^{13}C NMR spectrum, as well as displaying distinctive J_{CF} values as illustrated below (**Figure 2.14**). A point of note from carrying out ^{1}H NMR spectroscopy using different solvents is the "switching" of positions of the C(6')H and C(4')H signals. Following determination of the C(4')H and C(6')H signals in ^{1}H NMR spectrum of **79** using DMSO-d_6 as solvent (**Table 2.5**, entry 5, Method A) (δ_H 8.29 and 8.45 ppm for C(6')H and C(4')H respectively), analysis using $CDCl_3$ as solvent indicated the signal for C(4')H was identified at δ_H 7.94 ppm and the signal ascribed to C(6')H was observed at δ_H 8.22 ppm, while the splitting patterns remain the same (**Table 2.5**, entry 5, Method B).

In ^{13}C NMR spectroscopic analysis of **79**, the signals for the alkene C(2)H and C(5')H of the ring were observed as overlapping doublets at δ_C 122.6 ppm, providing carbon-fluorine coupling constants of $^{4}J_{CF}$ 2.6 Hz or 1.9 Hz. Analysis by ^{1}H–^{13}C HETCOR experiment also showed an overlap of these signals at δ_C 122.7 ppm. Further 2D NMR experiments such as ^{1}H–^{13}C HMBC would be required to distinguish between the carbon signals for C(2)H and C(5')H, but this was not undertaken in this work. The 2D NMR spectra from the experiments of **79** are included in *Appendix V*. The J_{CF} coupling values for **79** are in line with those obtained for other fluorine-substituted pyridine rings and are consistent with the observation that carbons in close proximity to the ring nitrogen have a larger carbon-fluorine coupling than analogous carbons further removed from the ring nitrogen.[66,67]

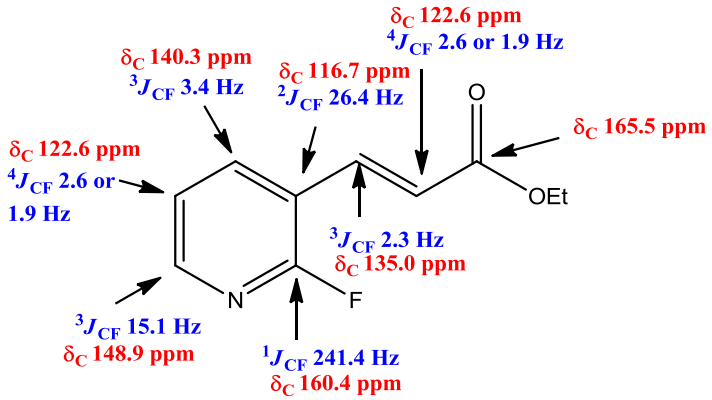
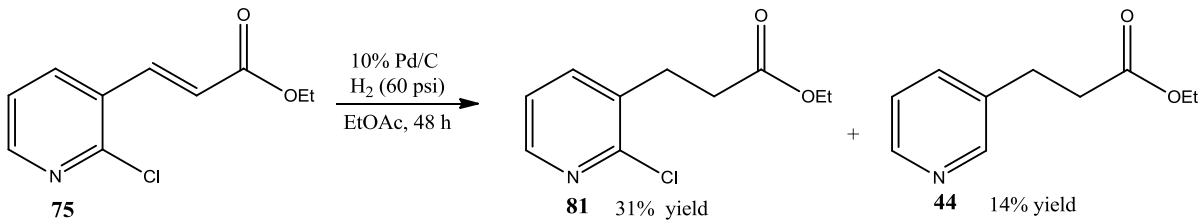


Figure 2.14: ^{13}C NMR values and J_{CF} values from ^{13}C NMR (75.5 Hz, DMSO-d_6) spectroscopy of 79 (Table 2.5, entry 5, Method A)

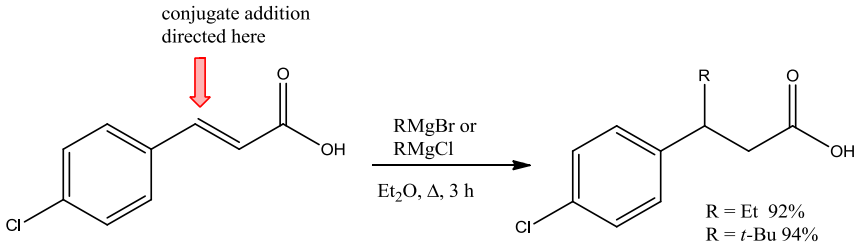
Formation of the saturated esters was examined by hydrogenation of the α,β-unsaturated esters using the literature procedure,[37] which had previously only been used in this work on unsubstituted pyridine systems (**Section 2.3.1.2.1**). Reaction conditions involved palladium on carbon (10%), ethyl acetate as solvent and the reaction carried out at different pressures of hydrogen, for different lengths of time depending on the substrate. Initial investigations of this procedure centred on hydrogenation of (*E*)-ethyl 3-(2-chloropyridin-3-yl)acrylate **75** and the reaction was deemed to be complete after 48 h as determined by ^{1}H NMR and infrared spectroscopic analysis. Following purification by column chromatography, two products were isolated; saturated ester **81** as the major product in 31% yield and the dehalogenated ester **44** as the minor component in 14% yield (**Scheme 2.33**).



Scheme 2.33

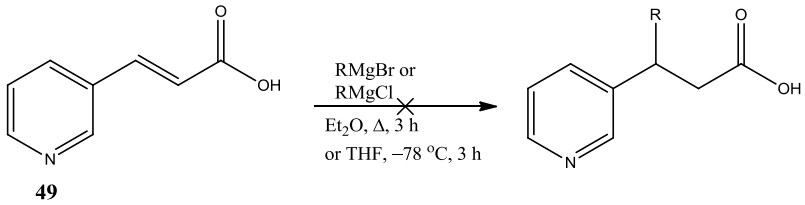
Despite repeating the hydrogenation, avoidance of the dehalogenation pathway proved challenging. Dehalogenation of aryl halides under hydrogenation conditions is well-established with displacement of chloride and bromine frequently observed.[11]

A strategy to circumvent the impasse of halogen expulsion involved conjugate addition of alkyl Grignard reagents to the 3-phenylpropenoic acids, providing β-substituted acids in excellent yield. Previous work in this laboratory has employed this approach to synthesise 3-alkyl-3-arylpropanoic acids,[8-10,12,17] with investigations by McNamara in the presence of various halogen groups of particular interest (**Scheme 2.34**).[11]



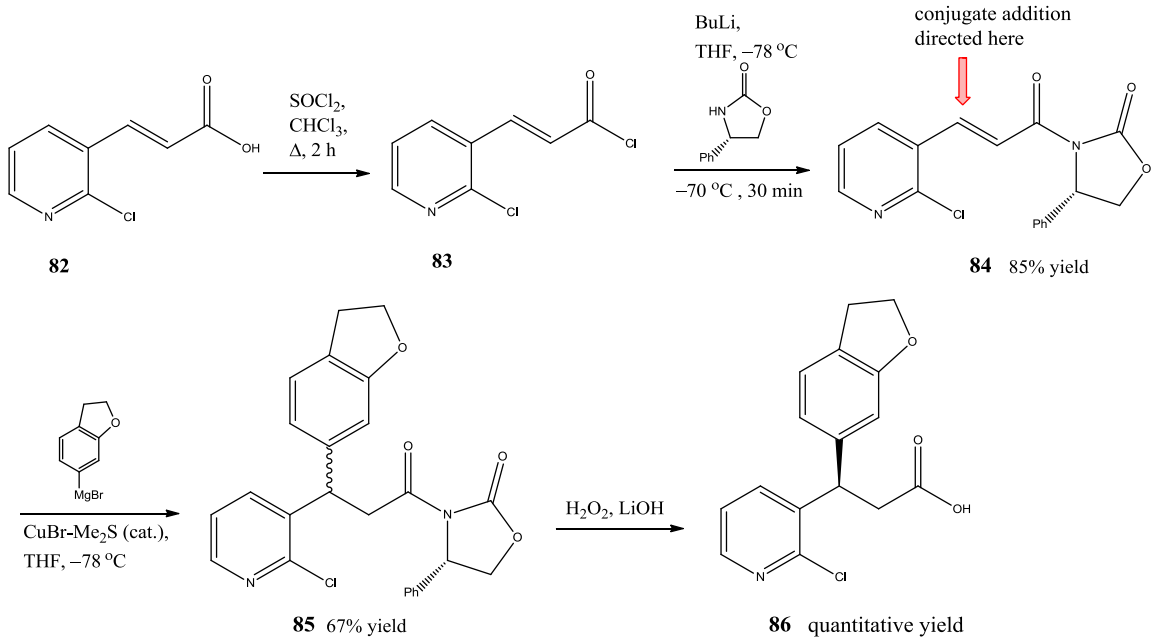
Scheme 2.34

Employment of these optimised conditions with unsubstituted acid **49** as a model system was unsuccessful; no trace of the anticipated β-alkylated acid was detected even after repeated efforts (**Scheme 2.35**).



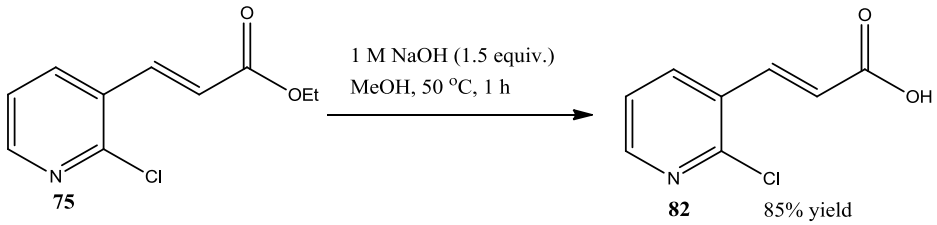
Scheme 2.35

In similar work by Kato *et al*.,[41] following formation of an acid chloride from carboxylic acid **82**, a chiral oxazolidinone moiety was tethered to acid chloride **83** to generate the *N*-acyloxazolidinone **84**. Subsequent stereoselective conjugate addition of the α,β-unsaturated imide with an aryl Grignard reagent furnished the β-substituted derivative **85** in good yield. This was followed by cleavage of the auxiliary to produce the enantioenriched carboxylic acid **86** (**Scheme 2.36**). This strategy of chiral oxazolidinones as enantiopure auxiliaries was pioneered in work by Evans in the late 1970's and early 1980's towards development of the enantioselective aldol reaction.[109-111]



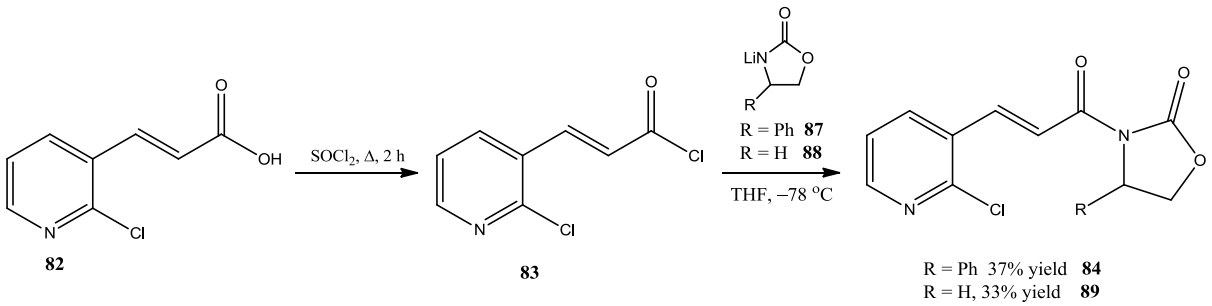
Scheme 2.36: Conjugate addition of Grignard reagents to alkene bond[41]

This procedure was next examined with a view to assembling the β-substituted pyridine derivatives in this project, enabling retention of the chlorine atom (**Scheme 2.37**). The first step involved hydrolysis of the ester **75** using aqueous sodium hydroxide in methanol at 50 °C employing Kato's procedure,[41] which afforded the carboxylic acid **82** in 85% yield.



Scheme 2.37

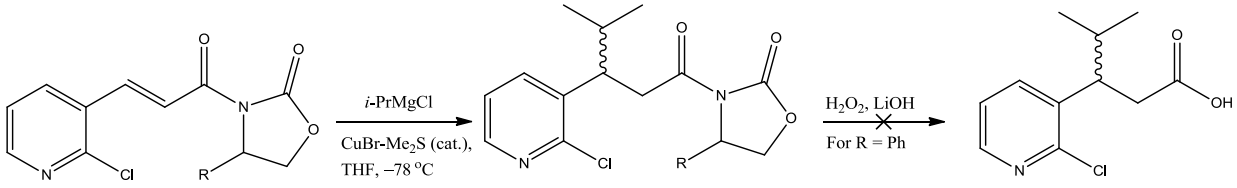
The α,β-unsaturated acid **82** was transformed to the acid chloride **83** using thionyl chloride under standard conditions, followed by reaction with the lithiated oxazolidinones **87** and **88**, as previously demonstrated by Kato,[41] to prepare the *N*-acyloxazolidinones **84** and **89** (**Scheme 2.38**). Formation of the *N*-acyloxazolidinones was successful, albeit in low yield. Analysis of **84** by ^{1}H NMR spectroscopy was consistent with previously reported data by Kato,[41] while the achiral acyloxazolidinone **89** was a novel compound.



82 83

Scheme 2.38

For the crucial conjugate addition, commercially available isopropylmagnesium chloride was used as the Grignard reagent (*cf.* usual procedure of fresh generation of the Grignard reagent as previously carried out in the Maguire group)[10,11,17] and the procedure repeated following conditions outlined by Kato.[41] Michael addition of the Grignard reagent to the achiral *N*-acyloxazolidinone **89** to afford **90** was unsuccessful; however, stereoselective 1,4-conjugate addition to **84** containing the chiral oxazolidinone auxiliary appeared to generate the β-substituted product **91** in 68% crude yield (**Scheme 2.39**). The crude material was not further purified but the product **91** was tentatively identified from nominal mass spectrometry. In analysis by mass spectrometry, the molecular ion displayed the characteristic 3 : 1 chlorine isotope pattern at m/z (ES+) 375.0 $\{[(C_{14}H_{17}{}^{37}ClN_2O_3)^+]$ 32%$\}$ and 373.1 $\{[(C_{14}H_{17}{}^{35}ClN_2O_3)^+]$ 100%$\}$.



R = H **89**
R = Ph **84**

R = H, not detected **90**
R = Ph 68% crude yield **91**

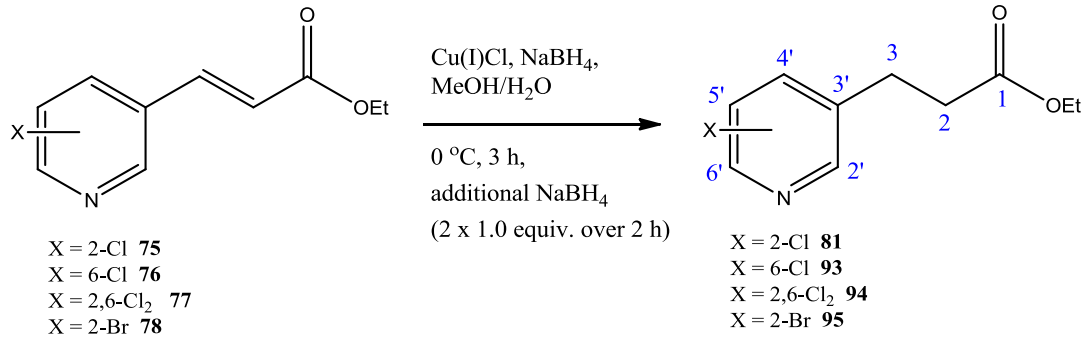
92

Scheme 2.39

The final deprotection step involving cleavage of the chiral auxiliary by lithium hydroxide and hydrogen peroxide (30%, 3 drops) did not proceed to furnish acid **92** under the conditions described by Kato,[41] instead a complex mixture was recovered (**Scheme 2.39**). This may be attributed to the fact that the material brought forward was not purified leading to a difficulty in isolating a clean sample of the deprotected product. This approach was not pursued any further.

Yoshizumi *et al*. have reported reduction of an alkene bond in the presence of a chlorine atom under mild conditions using sodium borohydride and copper(I) chloride, with no loss of the halogen.[112] In this work, the reduction of **75** was repeated as described by Yoshizumi (**Scheme 2.40**).[112] Purification by column chromatography afforded the pure saturated ester **81** in 45% yield (lit.,[112] 77% yield). The product was isolated with complete retention of the key halogen group, making it a feasible route to synthesise saturated pyridine esters

possessing a halogen substituent. This method was repeated in the preparation of **93** and **94**, and the esters were isolated in 66% and 50% yield respectively (**Table 2.6**, entries 2 and 3). Attempted reduction of unsaturated ester **78** (**Table 2.6**, entry 4) resulted in displacement of the labile bromine even under these mild reduction conditions. Following chromatography, saturated ester **95** was isolated in 11% yield and the dehalogenated compound **44** was isolated as the major component in 32% yield. The results are summarised below (**Table 2.6**).



X = 2-Cl **75**
X = 6-Cl **76**
X = 2,6-Cl_2 **77**
X = 2-Br **78**

X = 2-Cl **81**
X = 6-Cl **93**
X = 2,6-Cl_2 **94**
X = 2-Br **95**

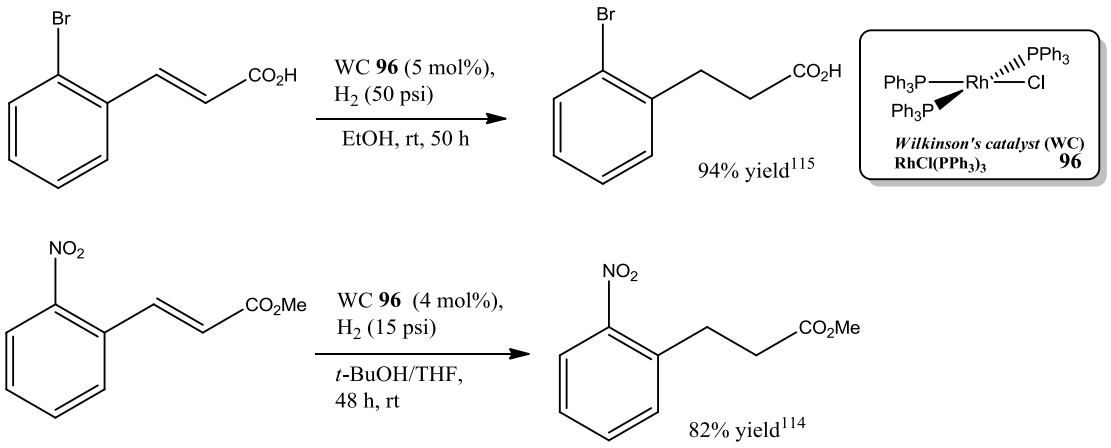
Scheme 2.40

Table 2.6 *Isolated yields of saturated esters **81**, **93-95** as well as isolation of dehalogenated ester **44***

Entry	X =	Unsaturated ester	Saturated ester	Yield (%)[a]
1	2-Cl	**75**	**81**[112]	45
2	6-Cl	**76**	**93**[113]	66
3	2,6-Cl_2	**77**	**94**	50
4	2-Br	**78**	**95**	11 + 32% of **44**

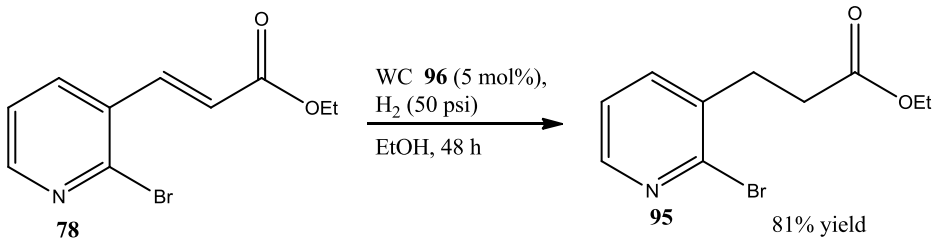
[a] Isolated yield after column chromatography

Wilkinson's Catalyst **96** has been reported to catalyse the hydrogenation of alkenes in the presence of nitro[114] and bromine groups (**Scheme 2.41**).[115] This is very important considering that the nitro group is one of the most easily reduced groups in organic synthesis and the intrinsic weak nature of the carbon–bromine bond (66 kcal/mol). Wilkinson's catalyst **96** is a red crystalline solid which exists as a square planar 16-electron complex.



Scheme 2.41: Hydrogenation using Wilkinson's catalyst 96 by Jourdant[114] and Kelly[115]

The hydrogenation of ester **78** was attempted using Wilkinson's catalyst employing the procedure outlined by Kelly (**Scheme 2.42**).[115] Reaction conditions consisted of dissolving the ester in ethanol followed by addition of catalyst **96**. A homogeneous solution was observed in the vessel due to the solubility of catalyst in the solvent, in contrast to the heterogeneous palladium on carbon catalyst. This mixture was shaken under hydrogen at 50 psi, for 48 h at room temperature. Removal of solvent under reduced pressure gave the saturated ester **95** as brown oil, which was isolated as a pale yellow oil in 81% yield after column chromatography. The structure of the desired ester was confirmed by ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, as well as nominal and high resolution mass spectrometry. The presence of two bromine isotopes (^{81}Br and ^{79}Br) was detected in a characteristic 1 : 1 ratio in both the nominal and high resolution mass spectrometric analysis. Hydrogenation of unsaturated ester **78** using Wilkinson's catalyst **96** is illustrated in the catalytic cycle below (**Figure 2.15**).



Scheme 2.42

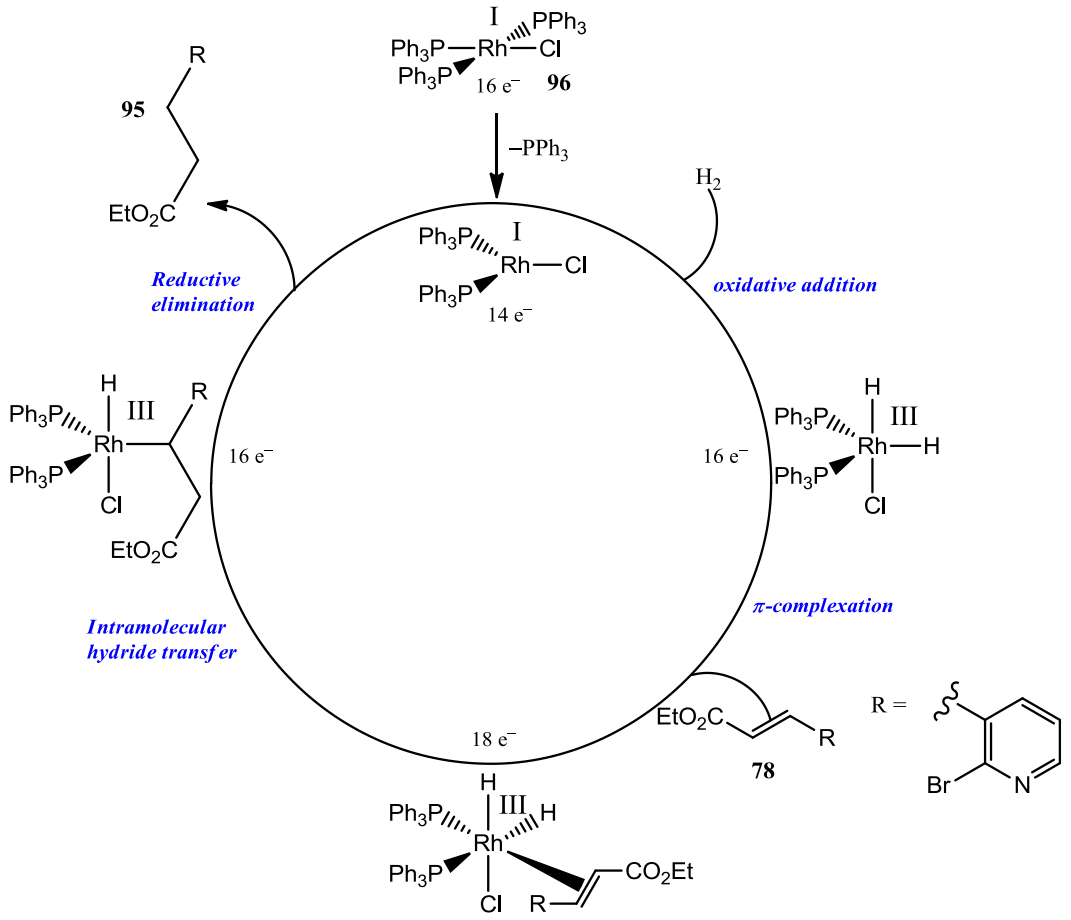
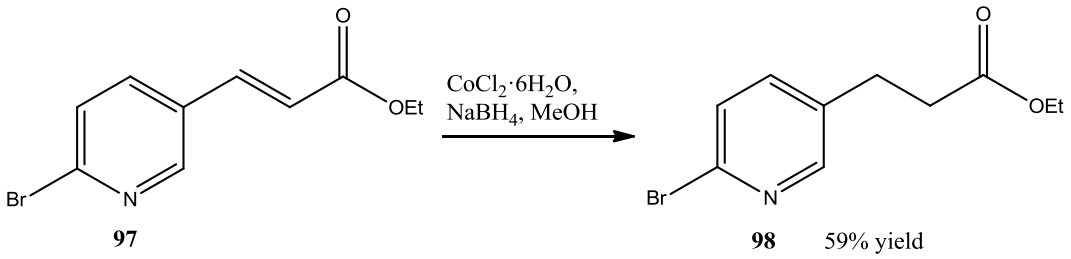


Figure 2.15: Catalytic cycle of hydrogenation of 78 using Wilkinson's catalyst 96

To the best of our knowledge, this is the first example of hydrogenation of pyridineacrylates containing a bromine substituent using Wilkinson's catalyst **96**. Since this work was undertaken, Ulven and co-workers have reported hydrogenation of the alkene bond of pyridineacrylate **97** using cobalt(II) chloride hexahydrate ($CoCl_2 \cdot 6H_2O$) and $NaBH_4$ to generate the saturated analogue **98**, while retaining the bromine substituent (**Scheme 2.43**)[116] (based on a method originally described by Satoh).[117]

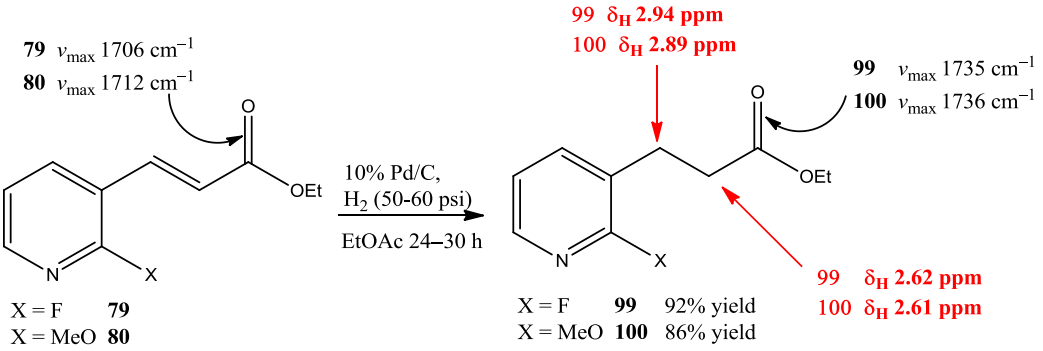


Scheme 2.43

The 2-fluorine and 2-methoxy substituted esters, **79** and **80** underwent hydrogenation using palladium on carbon (10%) as catalyst (**Scheme 2.44**). These substituents, unlike the easily displaceable chlorine and bromine atoms are not extruded under standard hydrogenation conditions. Hydrogenation of fluorine derivative **79** involved ethyl acetate as solvent,

palladium on carbon and hydrogen at 50 psi, for 30 h at room temperature. Reaction completion was confirmed by TLC analysis, ^{1}H NMR and infrared spectroscopy as illustrated below (**Scheme 2.44**). Analysis by ^{1}H NMR spectroscopy shows the expected disappearance of the doublets ascribed to the alkene signals and appearance of a pair of triplets at δ_H 2.62 ppm and δ_H 2.94 ppm accounting for the two methylene groups. The crude saturated fluorine ester **99** was isolated in 92% yield and was sufficiently pure to use without further purification.

In the hydrogenation of methoxy substituted ester **80**, similar conditions were employed [H_2, (60 psi)] and the reaction was deemed to be complete within 24 h as determined by ^{1}H NMR and infrared spectroscopic analysis (**Scheme 2.44**). The saturated methoxy ester **100** was obtained in 86% yield and was deemed clean enough to bring forward without additional purification.



Scheme 2.44

Thus, access to synthetically useful amounts of 3-pyridinepropanoate esters **81**, **93-95** and **99-100** was achieved, overcoming the competing dehalogenation reactions.

2.3.1.3.3 Generation of 3-pyridinepropanoic acids

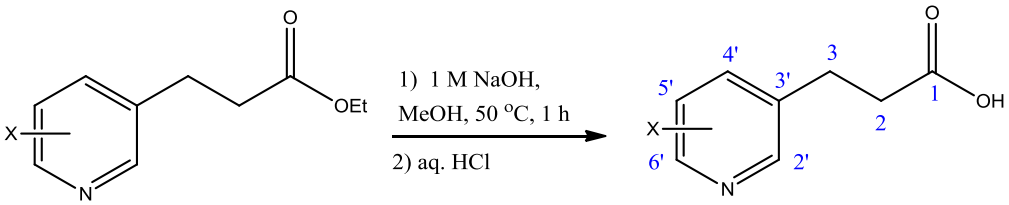
The next step involved the formation of 3-pyridylpropanoic acids which are suitable precursors for subsequent preparation of pyridyl substituted α-diazoketones. This was accomplished by two methods in this work; hydrolysis of the saturated ester derivatives **81**, **93-95** and **99-100** or hydrogenation of pyridineacrylic acids **110** and **114** using palladium on carbon. The pyridineacrylic acids **110** and **114** were prepared by Heck and Knoevenagel reactions respectively.

2.3.1.3.3.1 Hydrolysis of saturated esters

The hydrolysis followed the method laid out by Kato and co-workers [41] and involved heating a solution of ester and aqueous sodium hydroxide in methanol at 50 °C for 1 h (**Scheme 2.45**). This was followed by a basic workup using *tert*-butyl methyl ether (TBME) and aqueous sodium hydroxide. In the preparation of samples **103** and **105**, recovery was complicated due to hydrolysis of ethyl acetate used as workup solvent in place of TBME resulting in the formation of acetic acid (δ_H 2.10 ppm). The acetic acid was subsequently eliminated by

column chromatography furnishing the clean carboxylic acids **103** and **105**, though this had an adverse effect with lower yields obtained for these compounds. Accordingly, for the remainder of the hydrolysis reactions to prepare **101**, **102**, **104** and **106**, TBME was used in the first step of the workup and the products were sufficiently pure to use without further purification.

The isolated yields and melting points of the pyridine carboxylic acids **101-106** are summarised below (**Table 2.7**).



X = 2-Cl **81**
X = 6-Cl **93**
X = 2,6-Cl_2 **94**
X = 2-Br **95**
X = 2-F **99**
X = 2-MeO **100**

X = 2-Cl **101**
X = 6-Cl **102**
X = 2,6-Cl_2 **103**
X = 2-Br **104**
X = 2-F **105**
X = 2-MeO **106**

Scheme 2.45

Table 2.7 *Isolated yields and melting points of saturated acids* ***101-106***

Entry	Ester X =	Acid X =	m.p. (°C)	Yield (%)[a]
1	2-Cl **81**	2-Cl **101**	126–128	69
2	6-Cl **93**	6-Cl **102**	97–99	57
3	2,6-Cl_2 **94**	2,6-Cl_2 **103**[118]	153–156	51[b]
4	2-Br **95**	2-Br **104**	145–148	82
5	2-F **99**	2-F **105**[119]	100–102	53[b]
6	2-OMe **100**	2-OMe **106**[119]	112–114	58

[a] Crude yield of carboxylic acid.
[b] Isolated yield of carboxylic acid. Acetic acid was formed in the workup and was separated by column chromatography.

While the carboxylic acids **101**, **102** and **104** are novel compounds, preparation of **105** and **106** has been described by Denonne and co-workers *via* Heck reaction, followed by hydrolysis and hydrogenation,[119] however, without reporting characterisation. Accordingly, each of the compounds **101-106** was fully characterised using ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, melting point analysis, nominal and high resolution mass spectrometry, as well as elemental analysis and X-ray crystal structure determination in some cases. It should be noted that elemental analysis was attempted in all cases, though only carboxylic acids **102** and **103** gave accurate results for this analysis.

Huff and co-workers have previously synthesised 3-(2,6-dichloropyridin-3-yl)propanoic acid **103**, reporting melting point data as well as ^{1}H NMR and infrared spectroscopic analysis.[118] To complete characterisation of **103**, elemental analysis, melting point, ^{13}C NMR spectroscopy, nominal and high resolution mass spectrometry were recorded. Analysis by ^{1}H NMR and infrared spectroscopy was undertaken for comparison with work by Huff and excellent agreement was observed.[118] The melting point of 153–156 °C obtained was comparable to the literature value of 155–157 °C.[118] An X-ray crystal structure of acid **103** was also obtained, providing conclusive structural identity (**Figure 2.16**). In addition, solid state interactions of **103** included the distinctive $R_2^2(8)$ dimer pattern of carboxylic acids with hydrogen bond interactions of O–H···O at 1.88 Å. This designation for inter- and intramolecular interactions follows rules originally described by Etter,[120] with the eponymous rules a now a staple of modern solid state chemistry. Furthermore, a halogen bonding O···Cl interaction was identified with a distance of 2.97 Å.

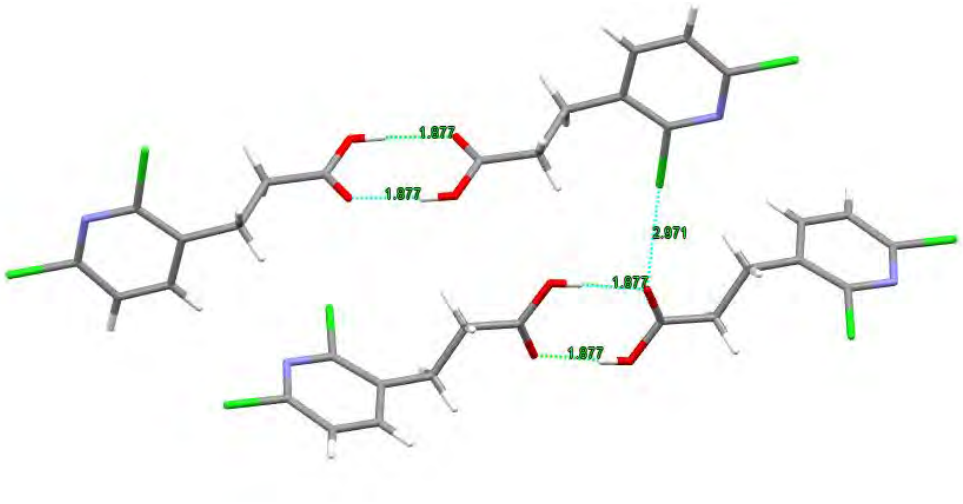
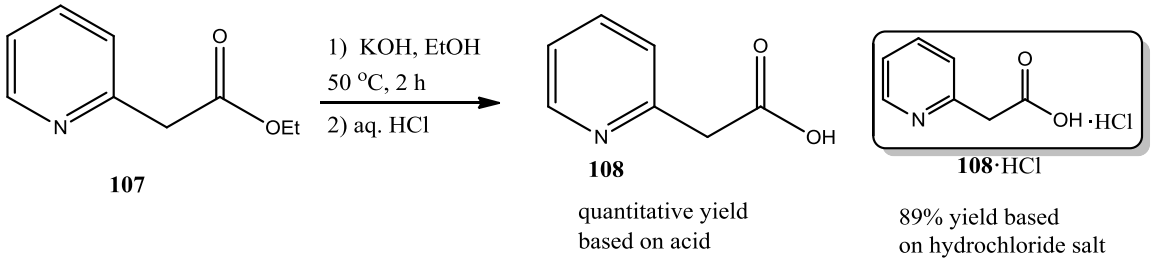


Figure 2.16: X-ray crystal structure of 103

Hydrolysis was also attempted on commercially available ethyl 2-(pyridin-2-yl)acetate **107**, though different reaction conditions were used following a reported procedure (**Scheme 2.46**).[121] The ^{1}H NMR spectroscopic data using DMSO-d_6 as solvent was in general accordance with formation of the acid **108** but was not consistent with values described by Salomé using DMSO-d_6 as NMR solvent.[121] The melting point obtained also differed as a higher value than the published data was identified, 149 °C *cf.* lit.,[121] 98 °C but this melting point was much closer to the corresponding hydrochloride salt, 135–137 °C.[122] This led to the unconfirmed conclusion that **108** was isolated as the hydrochloride salt **108**·HCl. This compound was prepared for use in benzotriazole-mediated reactions discussed later (**Section 2.3.2.1**).



107 **108** **108**·HCl

quantitative yield based on acid

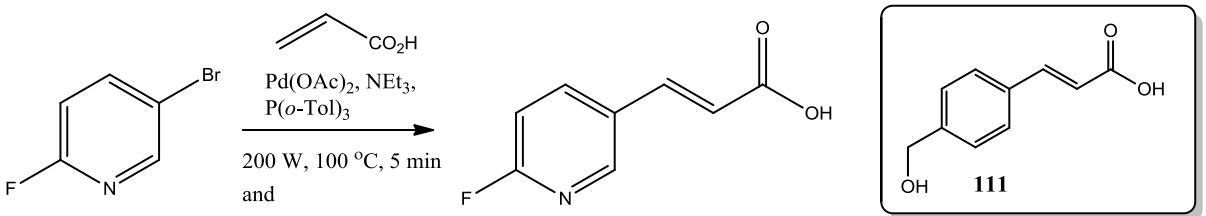
89% yield based on hydrochloride salt

Scheme 2.46

2.3.1.3.3.2 Synthesis and hydrogenation of 3-pyridylpropenoic acids

Heck reaction of commercially available 5-bromo-2-fluoropyridine **109** with acrylic acid was used to prepare *para*-fluoro substituted carboxylic acid **110**. Reaction conditions involved heating **109**, acrylic acid, tri(*o*-tolyl)phosphine and triethylamine under microwave irradiation as outlined by Denonne (**Scheme 2.47**).[119] A similar strategy has been applied previously in the Maguire research group by Foley for benzene analogues in the preparation of *p*-(hydroxymethyl)cinnamic acid **111**,[2] following a procedure originally described by Baudoin and co-workers.[123]

The halogenated pyridine **109**, palladium(II) acetate, triethylamine and acrylic acid were placed in a sealed 10 mL microwave vessel and the reaction mixture was heated and stirred for 5 min at 200 W at 100 °C, followed by an additional 6 min at 300 W at 100 °C. Since the method only permitted limited volumes of reagents for use in the reaction vessel, the procedure was repeated a further four times with all the filtered portions added together to give a final amount of sample for use in subsequent reactions. The synthesis of **110** has been described by Denonne and co-workers,[119] but once again no spectroscopic or physical data was reported. Further characterisation of **110** in this work involved analysis by ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, confirming its structure and successful synthesis. Subsequent efforts to repeat this procedure frustratingly failed to generate the desired product **110**, despite changing many variables of the reaction (*e.g.* starting materials, reaction conditions). However, the sample of **110** that was successfully isolated was brought forward for the subsequent hydrogenation step.

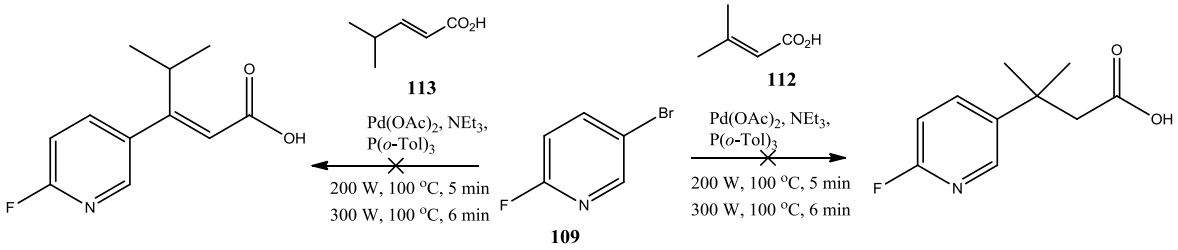


109 **110** quantitative yield **111**

Scheme 2.47

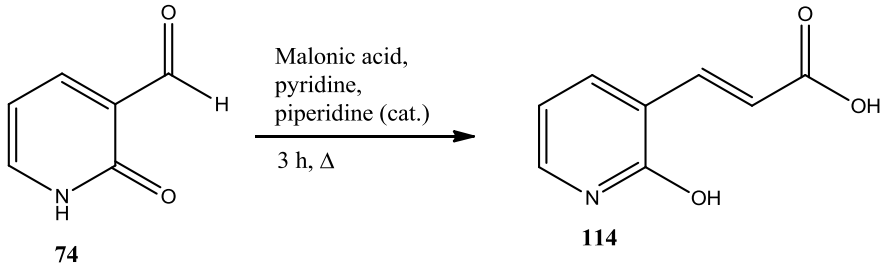
Use of the Heck reaction conditions to generate 3-substituted pyridinepropenoic acids was briefly explored as summarised in **Scheme 2.48** using 3-methylbut-2-enoic acid **112** and (*E*)-

4-methylpent-2-enoic acid **113** in place of acrylic acid, but this method failed to produce any of the anticipated Heck products (**Scheme 2.48**). In retrospect, acid **112** is incompatible with the Heck reaction as it does not posess a β-hydrogen and formation of the corresponding 3-pyridylpropenoic acid is not possible. Given the challenges in reproducing the synthesis of **110**, this strategy was not further pursued.



Scheme 2.48

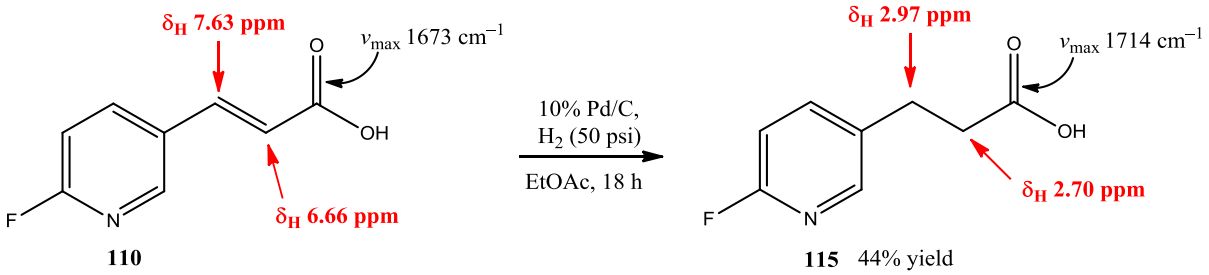
Synthesis of (*E*)-3-(2-hydroxypyridin-3-yl)acrylic acid **114** was conducted using the Knoevenagel reaction with pyridone aldehyde **74** following the method described by Queguiner (**Scheme 2.49**). [96] The pyridineacrylic acid **114** was isolated as a brown solid in quantitative recovery. Following literature precedent, the spectroscopic details are consistent with the pyridine tautomer,[96] although the sample also contained ~34 mol% of an intractable unknown impurity. The presence of this impurity may be attributed to the corresponding 2-pyridone tautomer but this is inconclusive and there is no spectroscopic data described for this compound. The melting point of **114** was also carried out, 290–291 °C (lit.,[96] >250 °C) . The material was brought forward for hydrogenation without further purification despite the presence of the unidentified impurity.



Scheme 2.49

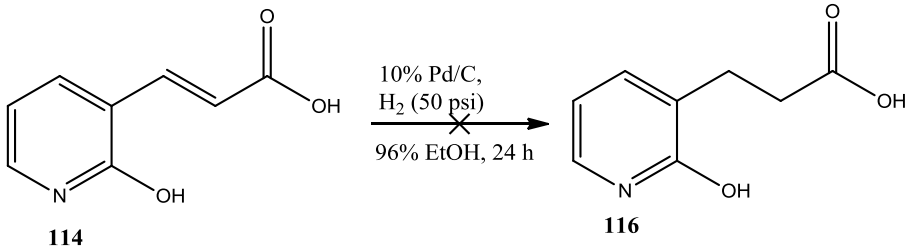
With the α,β-unsaturated acids **110** and **114** in hand, preparation of the corresponding propanoic acids *via* hydrogenation was next examined. For α,β-unsaturated acid **110**, hydrogenation involved using palladium on carbon (10%) with ethyl acetate as solvent and the mixture shaken under hydrogen at 50 psi (**Scheme 2.50**). The progress of the reaction was once again determined by TLC analysis, as well as ^{1}H NMR and infrared spectroscopy. The reaction was deemed to be complete after 18 h and following chromatography, the purified acid **115** was isolated in 44% yield as a dark red solid. As no spectroscopic details were reported for carboxylic acid **115**,[119] proton NMR, ^{13}C NMR and infrared spectroscopy along with nominal and high resolution mass spectrometry was carried out, which were consistent with generation of the hydrogenated acid **115**. The signals for the pyridine protons were

consistent with retention of the fluorine atom and J_{CF} coupling values were also observed in the ^{13}C NMR spectrum of **115**.



Scheme 2.50

Hydrogenation of (*E*)-3-(2-hydroxypyridin-3-yl)acrylic acid **114** to provide saturated analogue **116** proved substantially more challenging than expected (**Scheme 2.51**). The difficulty encountered involved insolubility of the pyridineacrylic acid in a range of solvents including ethyl acetate, methanol, ethanol, 96% ethanol, tetrahydrofuran, and dichloromethane. Since 96% ethanol appeared to be the best choice from the solvents investigated, hydrogenation of the acid **114** suspended in 96% ethanol was attempted without success. Analysis showed that the crude mixture consisted of starting material only, with the presence of the alkene peaks still evident in the ^{1}H NMR spectrum.



Scheme 2.51

Alternative strategies which might be envisaged would include use of pyridine as a solvent for **114**, as Queguiner and co-workers have described reaction of **114** with pyridine and aqueous hydrochloric acid; use of Wilkinson's catalyst **96** which had worked effectively in the hydrogenation of **78**; hydrogenation of the ester of **114** formed either by esterification or from **74** using the Horner-Wadsworth-Emmons approach.

At this stage, samples of each of the carboxylic acids **101-106** and **115** had been successfully prepared as substrates for α-diazoketone synthesis (**Figure 2.17**). Carboxylic acids **101**, **102** and **104** are novel compounds, while preparation of acids **103-106** and **115** has previously been described.[118,119] However, although compounds **103-106** and **115** have previously been reported in the literature, their spectral characterisation has been undertaken here for the first time. In addition, many novel precursors were generated in the preparation of these acids and some compounds, previously identified in the literature, were fully characterised here for the first time.

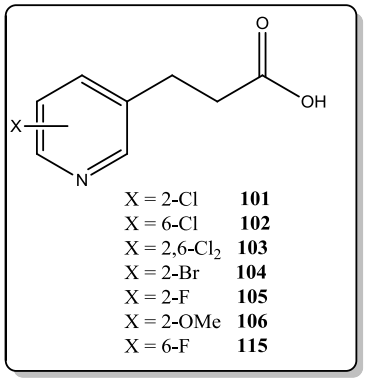


Figure 2.17

2.3.1.4 Preparation of substituted 3-pyridinecarboxylic acids by alkylation/benzylation

Having successfully achieved formation of α-diazoketones **63-65** bearing halogen substituents (see **Section 2.3.1.2.2**), extension to the synthesis of pyridine α-diazoketones using alternative 3-pyridylcarboxylic acids was undertaken. Oxygen and sulfur substituents were used in place of the halogens to explore whether the analogous α-diazoketones could be obtained in this work (**Figure 2.18**).

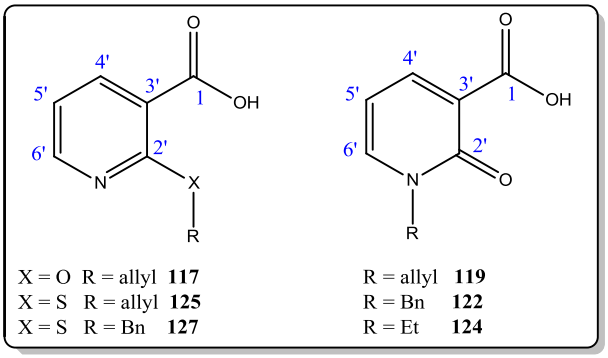


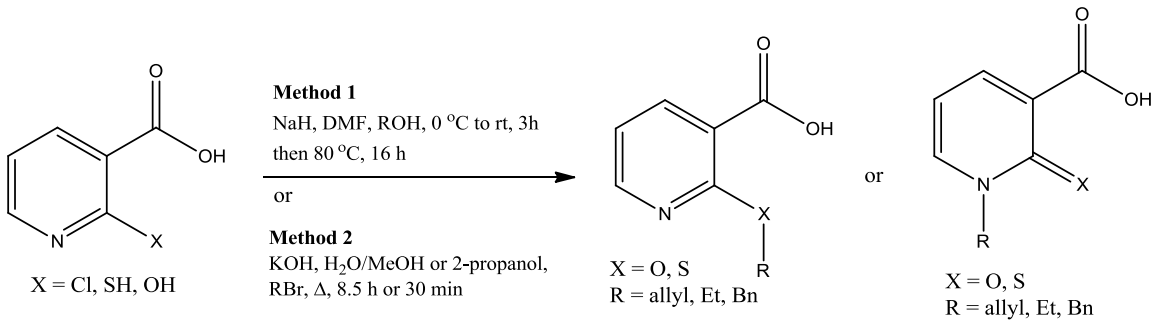
Figure 2.18

Thus, effort next turned towards the formation of substituted 3-pyridylcarboxylic acids. In this work, two synthetic approaches were explored;

1) Substitution of 2'-halogenated derivative **57** with an alkoxide or,

2) Alkylation/benzylation of 2'-O–H or S–H groups with an alkyl or benzyl bromide.

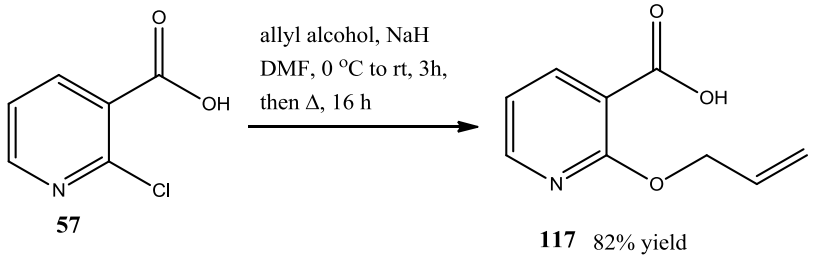
During the course of this work, the unanticipated *N*-alkylated pyridone acids **119**, **122** and **124** were also prepared and attracted our interests as substrates for α-diazoketone synthesis. The overall synthetic strategy is summarised below (**Scheme 2.52**).



Scheme 2.52

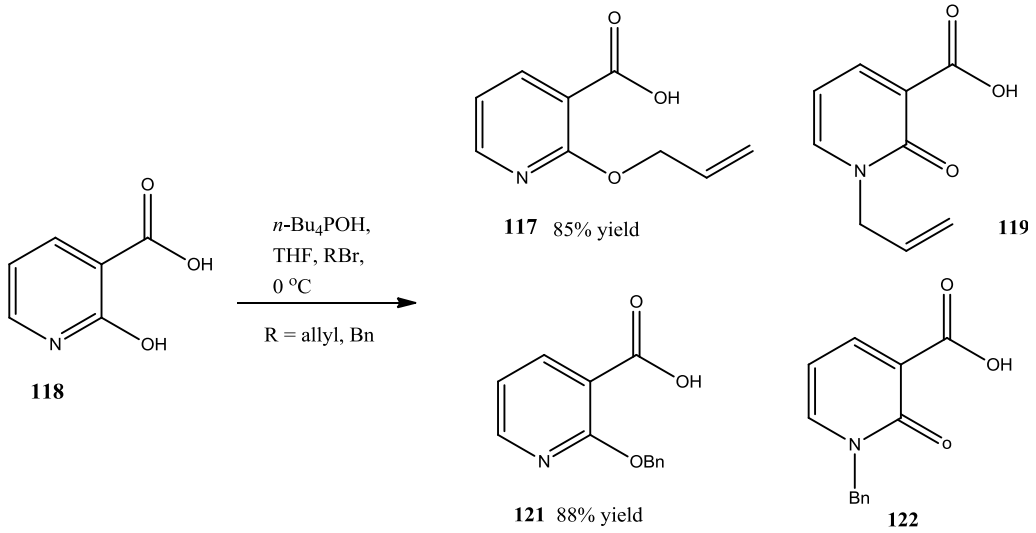
Method 1 was first investigated since a suitable substrate, 2-chloronicotinic acid **57**, was readily available. A procedure outlined by Sieburth involved reaction of 2-chloronicotinic acid **57** using allyl alcohol and sodium hydride in dimethylformamide to furnish the allyl ether **117**.[124] However, Sieburth *et al*. did not disclose yields or report spectroscopic data for the *O*-allyl acid **117**.

In the current investigation, employing the procedure described by Sieburth,[124] the *O*-allyl acid **117** was prepared in 82% yield in excellent purity and required no further purification (**Scheme 2.53**). The melting point of **117** was also recorded (160–162 °C).



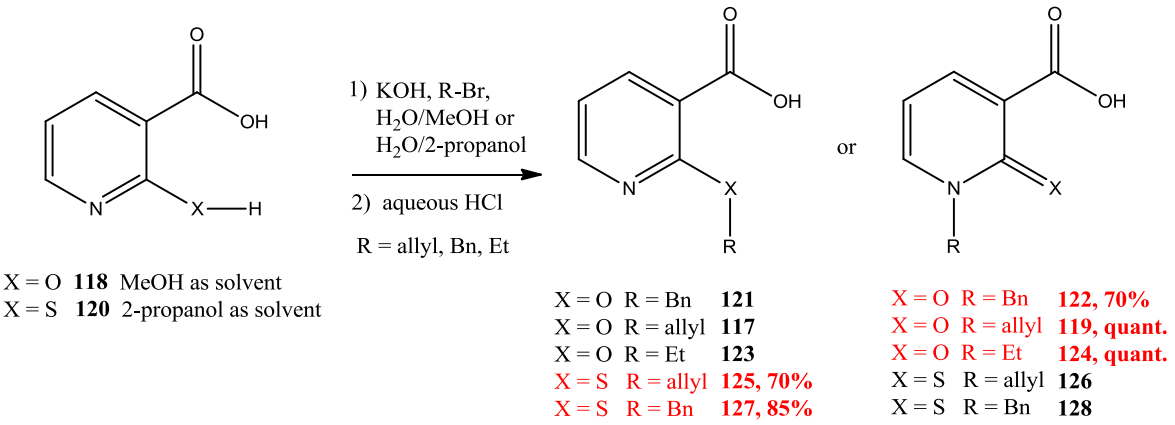
Scheme 2.53

More recently, Liu and co-workers have reported the synthesis of *O*-allyl substituted acid **117** in 85% yield and the *O*-benzyl acid **121** in 88% yield *via* method 2 employing 2-hydroxynicotinic acid **118**, allyl bromide or benzyl bromide and phase-transfer catalyst tetrabutylphosphonium hydroxide (**Scheme 2.54**).[125] However, as discussed later, comparison of Liu's data with our results suggests that Liu's interpretation is incorrect and the compounds actually formed are the *N*-alkylated tautomers **119** and **122**.[125] In contrast, Masu and co-workers have reported *N*-benzylation with the same substrate.[126]



Scheme 2.54: Work carried out by Liu[125]

The remainder of the target acids **119**, **121-128** were prepared by method 2, through alkylation and/or benzylation of the free O–H or S–H bond by alkyl bromides and benzyl bromide. In the present investigation, 2-hydroxynicotinic acid **118** and 2-mercaptonicotinic acid **120** served as substrates for the alkylation and/or benzylation reactions. Employing 2-hydroxynicotinic acid **118** as substrate, a procedure reported by Masu to synthesise **122** was utilised.[126] In the preparation of the sulfur substituted acids, a method outlined by Furdas and co-workers in their preparation of carboxylic acid **127** was followed.[127] The generation of functionalised 3-pyridine- and 3-pyridonecarboxylic acids along with their respective yields is summarised below, while the compounds isolated in this work are highlighted in red (**Scheme 2.55**).



Scheme 2.55

An important consideration is the existence of tautomers for 2-hydroxypyridine derivatives *e.g.* 2-hydroxynicotinic acid **118**. This is a classic example of tautomerism; the acid **118** exists in equilibrium between the hydroxyl and pyridone tautomers. It is observed that the keto pyridone form predominates in the solid phase while the hydroxyl form is favoured in the gaseous phase.[128-131] The equilibrium is found to be highly solvent dependent as the pyridone

form is favoured in polar solvents, and conversely, the formation of 2-hydroxypyridines is favoured in non-polar solvents such as petroleum ether.[128,132-135]

Katritzky has extensively discussed tautomerism involving hydroxyl, amino and mercaptopyridines, as shown below (**Figure 2.19**).[1] In the case of the hydroxyl- and mercaptopyridines, the pyridone and thione tautomers are more favoured than the free hydroxyl and thiol tautomeric forms, in contrast to the amino derivatives.

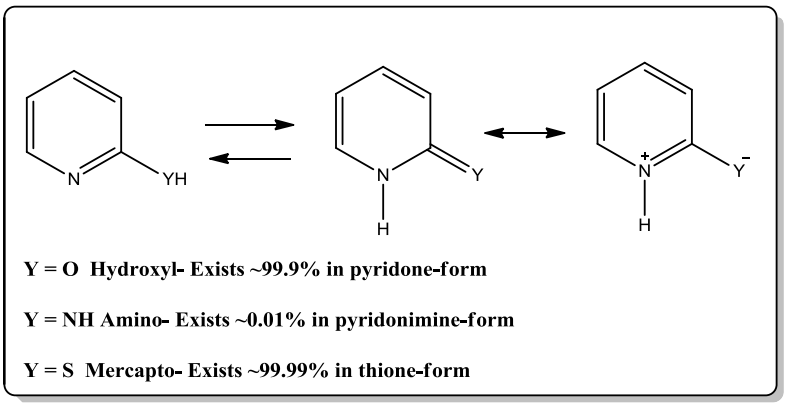
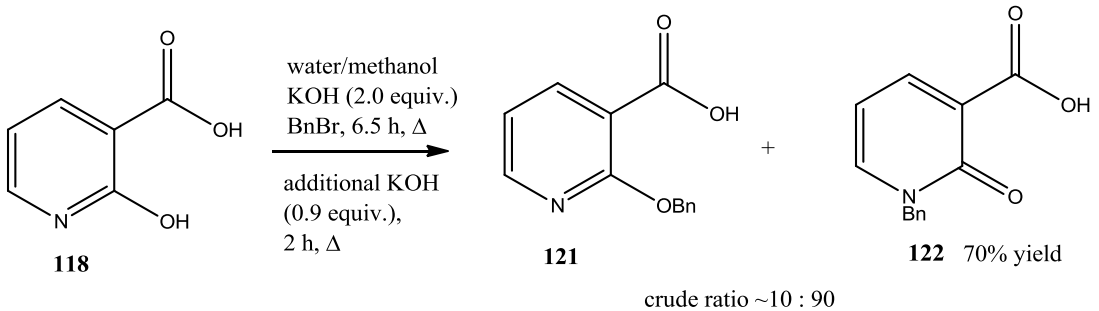


Figure 2.19 Tautomerism in hydroxyl-, amino- and mercaptopyridines[1]

Since there are two tautomeric forms of 2-hydroxynicotinic acid **118**, there are two potential products resulting from its benzylation; the *O*-substituted derivative **121** and the corresponding *N*-substituted compound **122**.

Masu and co-workers have reported the preparation of 1-benzyl-2-oxo-dihydropyridine-3-carboxylic acid **122** in 93% yield *via* benzylation of carboxylic acid **118**. However, no spectroscopic data was recorded for this compound.[126] Masu's method was utilised in this work and involved addition of acid **118** to a solution of water/methanol and potassium hydroxide. Neat benzyl bromide was added dropwise to the reaction mixture which was heated under reflux for 6.5 h initially, followed by introduction of additional potassium hydroxide (0.9 equiv.) and heated under reflux for a further 2 h (**Scheme 2.56**).



Scheme 2.56

Analysis of the crude mixture by ^{1}H NMR and ^{13}C NMR spectroscopy indicated the presence of both benzyl substituted compounds, with signals in the ^{13}C NMR spectrum at δ_C 65.4 ppm

and δ_C 53.2 ppm accounting for the benzylic methylene group of the *O*-benzyl acid **121** and *N*-benzyl acid **122** respectively. The identification of **121** and **122** was established by comparison with related benzyl substituted pyridines in the literature.[136,137] Following purification by column chromatography, the least polar fraction from the column was an impure sample of the *O*-benzyl derivative **121** and while mixed fractions were also obtained, the *N*-benzyl compound **122** was isolated as the most polar fraction recovered in 70% yield by flushing the column with ethyl acetate.

Infrared spectroscopic analysis assisted in determining the identity of **122**, as a stretching frequency was observed at ν_{max} 1630 cm^{-1}, which is indicative of the presence of a pyridone ring. Proton NMR spectroscopic data was not previously reported for this compound and the benzylic methylene group, $NC\underline{H}_2C_6H_5$, was observed at δ_H 5.27 ppm. Analysis by ^{13}C NMR spectroscopy was also carried out providing a characteristic value of δ_C 53.2 ppm, accounting for $NC\underline{H}_2C_6H_5$. In contrast, Sieburth disclosed ^1H and ^{13}C NMR data for the *O*-Bn acid **121**, synthesised by reaction of 2-chloronicotinic acid **57** and benzyl alcohol, with the characteristic benzylic signals identified at δ_H 5.65 ppm and δ_C 69.4 ppm.[124] The melting point obtained was in good agreement with Liu's reported value for **121**, 125–128 °C *cf.* lit.,[125] 130 °C, although we believe he had incorrectly assigned the structure. Interestingly, the data attributed to the *N*-benzyl acid **122** in this work correlated very well with data disclosed in error for the *O*-benzyl acid **121** by Liu *et al*. in their work.[125] The formation of *N*-benzyl acid **122** was confirmed by X-ray crystallographic structure determination (**Figure 2.20**). Interestingly, an S(6) intramolecular H–bond, which is highly favoured interaction, is observed for the X-ray crystal structure of **122** (1.63 Å).

Figure 2.20: X-ray crystal structure of *N*-benzyl acid 122

Upon close examination of the literature and building on the results obtained in this work (**Section 2.3.1.3.1**, **Section 2.3.2.2**–**2.3.2.4**), there is clear evidence for the formation of *N*-substituted derivatives **119** and **124** when 2-hydroxynicotinic acid **118** was used as starting material, whereas attempted alkylation and/or benzylation involving 2-mercaptonicotinic acid **120** as starting material afforded the *S*-substituted compounds **125** and **127** only.

Each of the alkyl and benzyl substituted acids **119**, **124**, **125** and **127** were prepared in high yields (**Scheme 2.55**) and were in good agreement with the literature data.[125,127,138] While we had anticipated accessing acids **117** and **121** following Liu's report of their synthesis,[125] we have confirmed that in practice the *N*-alkylated isomers **119** and **122** were recovered. As we had previously synthesised *O*-allyl acid **117** *via* an unambiguous route (**Scheme 2.53**), comparison of the spectroscopic data confirmed that the product isolated is the *N*-allyl derivative **119** and not the *O*-allyl acid **117**. ^{1}H NMR spectroscopy of *N*-allyl substituted acid **119** was markedly different than recorded for **117**, as the methylene group in the α-position to the heteroatom, NC$\underline{H}_2$CHCH_2, was located at δ_H 4.72 ppm for **119**, while compound **117** gave a value of δ_H 5.12 ppm for OC$\underline{H}_2$CHCH_2.

The stacked ^{1}H NMR spectra below illustrate the different chemical shifts of *O*-allyl substituted acid **117** in red and the *N*-allyl acid **119** in blue (**Figure 2.21**).

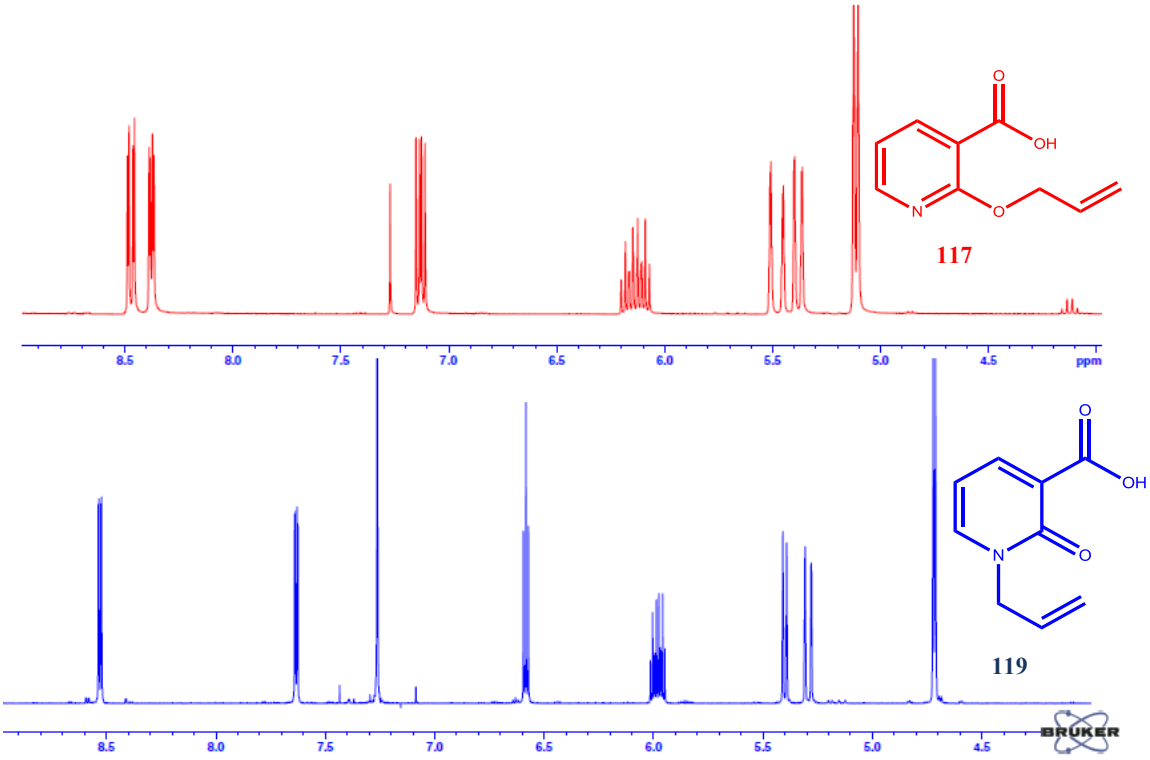


Figure 2.21: Stacked ^{1}H NMR spectra of 117 (300 MHz, $CDCl_3$) and 119 (600 MHz, $CDCl_3$)

The ^{13}C NMR spectroscopic data for **119** also correlated very well with the assignment of the *N*-allyl acid as the methylene group, NC$\underline{H}_2$CHCH_2, was seen at δ_C 52.0 ppm. Conclusive assignment of signals in the ^{1}H NMR and ^{13}C NMR spectrum of **119** was aided by ^{1}H–^{13}C HMBC and ^{1}H–^{13}C HSQC experiments (see *Appendix V*). This helped to differentiate between signals for C(4')$\underline{H}$ at δ_H 8.53 ppm and C(6')$\underline{H}$ at δ_H 7.63 ppm, which possessed similar coupling constants, *J* 7.2 and 2.2 Hz *cf.* *J* 6.7 and 2.2 Hz respectively. The assignment of signals for C(4')$\underline{H}$ and C(6')$\underline{H}$ in the ^{1}H NMR spectra of **122** and **124**, as well as signals in

the ^{13}C NMR analysis of **122** and **124** were assigned on the basis of the 2D NMR experiments undertaken for **119**.

Alkylation at the nitrogen was also observed with ethyl bromide to lead to the *N*-ethyl acid **124**, as the melting point obtained was far higher than the literature value for the *O*-ethyl substituted acid **123**, 168–170 °C *cf.* lit.,[139] 87.5–89 °C, but in close agreement with melting point for the *N*-alkylated analogue **124**, lit.,[138] 174 °C. While no spectroscopic details were disclosed by Okabayashi for *N*-ethyl acid **124**,[138] ^{1}H NMR spectroscopic analysis in this work provided signals which were consistent with the aromatic signals obtained for *N*-alkylated acids **119** and **122**. An X-ray crystal structure also confirmed alkylation at the nitrogen in preference to the oxygen (**Figure 2.22**) and similar to the *N*-benzyl acid **122**, an S(6) H–bonding interaction was observed for the pyridone acid **124** (1.71 Å).

Figure 2.22: X-ray crystal structure of *N*-ethyl acid 124

In contrast to the reactions using 2-hydroxynicotinic acid **118** which led to *N*-alkylation, with 2-mercaptonicotinic acid **120**, allylation and benzylation occur at the sulfur as summarised in **Scheme 2.55** and in agreement with literature reports.[127]

Following Furdas' procedure,[127] the *S*-benzyl acid **127** was prepared in 85% yield after recrystallisation from ethanol (**Scheme 2.55**). Proton NMR spectroscopic analysis of **127** using DMSO-d_6 as solvent was consistent with data reported by Furdas (DMSO-d_6 as solvent)[127] and by Wright and co-workers ($CDCl_3$ as solvent),[140] although the melting point analysis was not in complete agreement, 180–182 °C *cf.* lit.,[127] 192–194 °C. The novel *S*-allyl acid **125** was isolated in 70% yield employing similar reaction conditions (**Scheme 2.55**).[127]

An X-ray crystal structure of 2-(allylthio)nicotinic acid **125** was obtained. This acid also existed as $R_2^2(8)$ dimers with five dimeric units located in the unit cell (**Figure 2.23**). This is because there are five crystallographically independent molecules in the asymmetric unit. Thus, there are different H–bonding distances [1.83 and 1.79 Å (blue-green) *vs.* 1.80 and 1.75 Å (red-purple) *vs.* 1.75 and 1.75 Å (yellow)] (**Figure 2.24**).

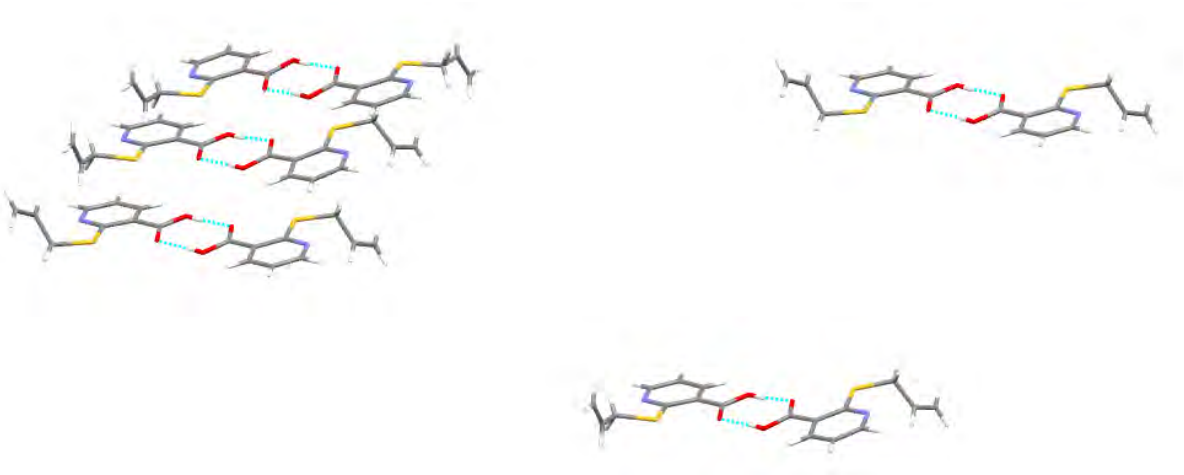


Figure 2.23: X-ray crystal structure of 2-(allylthio)nicotinic acid 125

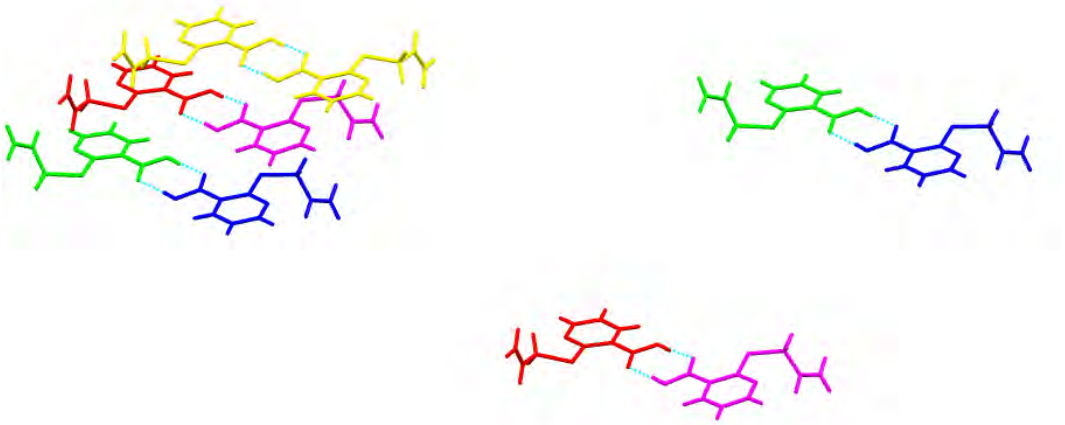
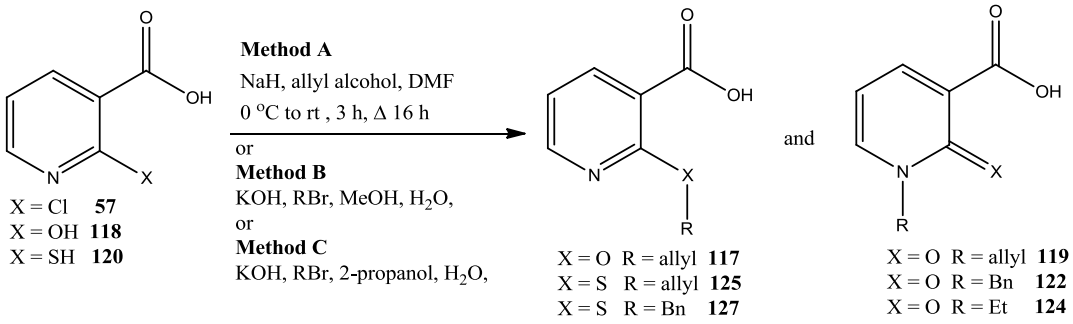


Figure 2.24: Centrosymmetric dimers packing in the unit cell of acid 125 with illustration of five distinct symmetry equivalence forms

A summary of the alkylation/benzylation reactions undertaken in this work is shown below (**Table 2.8**).

Table 2.8 *Isolated yields of substituted 3-pyridine- and 3-pyridonecarboxylic acids*



Entry	Acid starting material	Method	R	*O/S*-alkyl acid	*N*-alkyl acid	Yield (%)[a]
1	**57**	A	allyl	**117**[124,125]	–	82
2	**118**	B	allyl	–	**119**	quant.
3	**118**	B	Bn	–	**122**[126]	70[b]
4	**118**	B	Et	–	**124**[138]	quant.
5	**120**	C	allyl	**125**	–	70
6	**120**	C	Bn	**127**[127,140]	–	85

[a] Crude yield of carboxylic acid.
[b] Isolated yield after column chromatography.

As summarised in **Table 2.8**, six acids **117**, **119**, **122**, **124**, **125** and **127** were prepared, three of which are the pyridone tautomers while the remaining three are pyridine tautomers. Five of these acids **117**, **122**, **124**, **125** and **127** were explored as substrates for acylation of diazoalkanes.

2.3.1.5 Synthesis of α-diazoketones and α-diazo-β-ketoesters

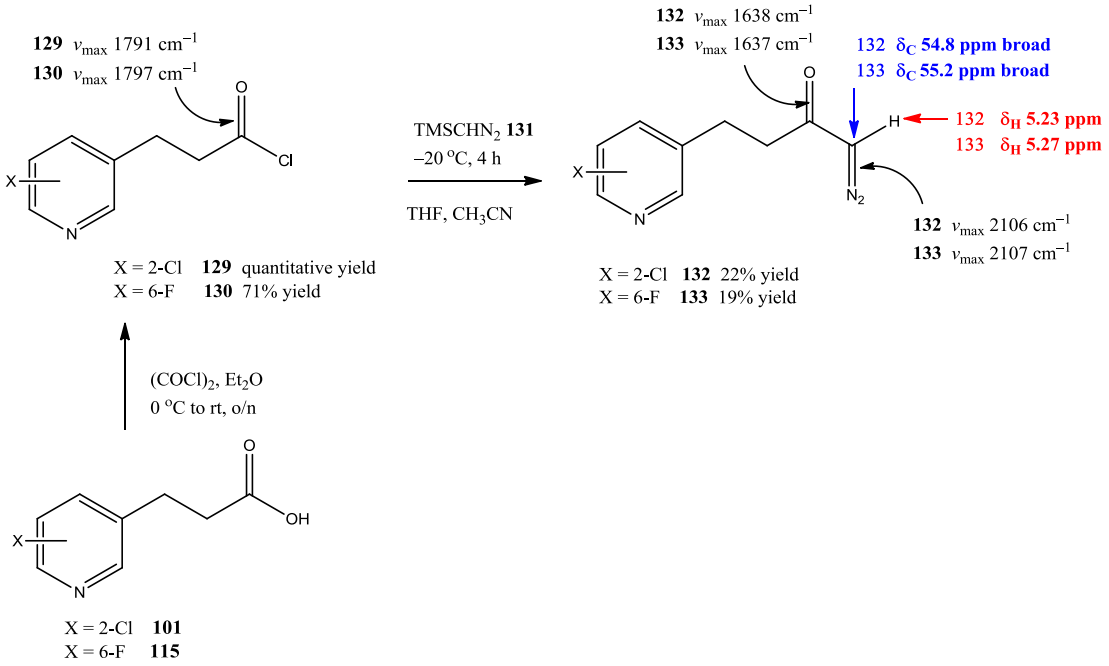
Three methods were explored to prepare pyridine substituted α-diazoketones in this work:

- Acylation of diazoalkane (trimethylsilyldiazomethane or diazoethane) using acid chloride[10-12,17,141] or unsymmetrical anhydride intermediates,[25,52,142] or
- alkylation of a pyridine thiol with an α-bromo-α'-diazoketone,[143] or
- Fukuyama's procedure involving alkylation of a pyridine alcohol using bromoacetyl bromide followed by treatment with *N*,*N'*-ditosylhydrazine.[144]

The pyridine-containing α-diazo-β-ketoesters were generated *via* a one-pot procedure using acid chlorides and commercially available ethyl diazoacetate.[64,145]

2.3.1.5.1 Formation of α-diazoketones via *acylation of diazoalkanes*

Having previously demonstrated successful synthesis of pyridine acid chlorides and α-diazoketones when the pyridine ring was halogenated (see **Section 2.3.1.2.2**), application of a similar strategy to access α-diazoketones from 3-pyridylpropanoic acid was next investigated. A well-established procedure in the Maguire research group using oxalyl chloride was employed with 3-pyridylpropanoic acids **101** and **115**,[9,11] providing the crude acid chlorides in good yields (**Scheme 2.57**). Formation of acid chlorides **129** and **130** was confirmed by infrared spectroscopy, with the characteristic acid chloride peaks observed at ν_{max} 1791 and 1797 cm^{-1} for **129** and **130** respectively.



Scheme 2.57: Infrared spectroscopic values of 129, 130, 132 and 133 as well as ^{1}H NMR (300 MHz, $CDCl_3$), ^{13}C NMR (75.5 MHz, $CDCl_3$) values of 132 and 133

The next step involved acylation of trimethylsilyldiazomethane ($TMSCHN_2$)[146-148] **131** using acid chlorides **129** and **130**. Diazomethane **15** or diazoethane **20** are traditionally employed as diazoalkane for the acylation but the commercially available $TMSCHN_2$ **131** was employed in this case. $TMSCHN_2$ is reported to be easier to handle than other diazoalkanes, though drawbacks include expense of material, contamination with α-TMS ketone of the product[149] and degradation of material in direct sunlight. While use of $TMSCHN_2$ has primarily focused on methylation reactions,[146-148] acylation of this compound to prepare terminal α-diazoketones has been demonstrated by Dolenc[142] using unsymmetrical anhydrides, while Makhey[141] and O'Neill[12] have employed acid chloride intermediates.

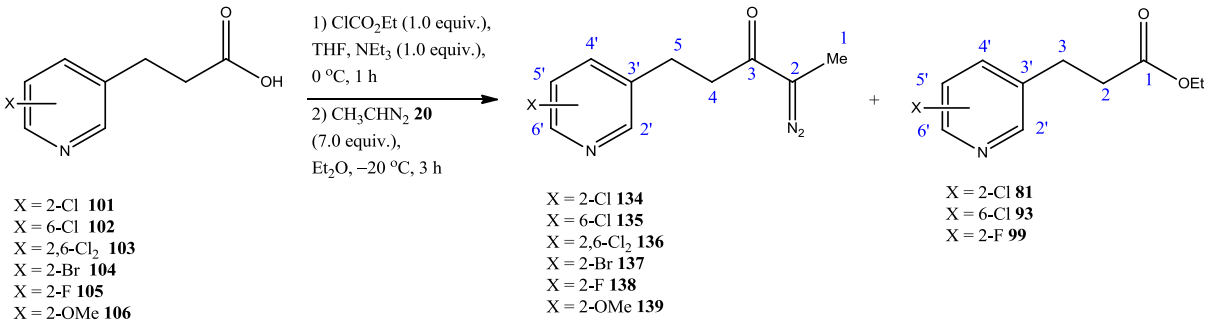
Employing a method described by Makhey and co-workers,[141] a tetrahydrofuran solution of acid chloride **129** or **130** was added slowly to a stirring solution of **131** in tetrahydrofuran/acetonitrile at –20 °C and the reaction mixture was stirred at this temperature

for 4 h (**Scheme 2.57**). Each of the terminal α-diazoketones **132** and **133** was obtained as a bright yellow oil after purification by column chromatography in low yields. The identity of the terminal α-diazoketones **132** and **133** was confirmed by infrared (ν_{max} 2106 and 2107 cm^{-1} respectively), ^{1}H NMR ($C\underline{H}N_2$ at δ_H 5.23 and 5.27 ppm respectively) and ^{13}C NMR ($\underline{C}HN_2$ at δ_C 54.8 and δ_C 55.2 ppm respectively) spectroscopic analysis. The spectroscopic data were consistent with data seen for the analogous phenyl substituted terminal α-diazoketones previously synthesised in the Maguire research group.[12,25,52] In the nominal mass spectrum of each of **132** and **133**, the molecular ion was successfully identified; in the high resolution mass spectrum, the ion following extrusion of nitrogen was identified in each case in a similar same way to α-diazoketones **63-65** investigated earlier (see **Section 2.3.1.2.2**).

Isolation and characterisation of the terminal α-diazoketones **132** and **133** demonstrates for the first time in this work that pyridyl α-diazoketones could be prepared with a flexible linker chain and were sufficiently stable to isolate and characterise.

In contrast to the nicotinoyl chlorides which are stable and commercially available, the pyridinepropanoyl chlorides **129** and **130** were susceptible to hydrolysis with **129** reverting back to the acid **101** on storage in the freezer for ~1 week. Attempts to repeat this procedure proved inconsistent, presumably due to the lability of the acid chlorides. Accordingly, use of the unsymmetrical anhydrides was next explored. While this procedure proved ineffective for pyridine acids **12** and **47** (see **Section 2.3.1.2.2**), this approach proved more successful with the halogen and methoxy substituted 3-pyridinepropanoic acids **101-106**. The procedure employed in this work was a modification of the protocol used by Dolenc and co-workers in the preparation of terminal α-diazoketones *via* unsymmetrical anhydrides.[142] Previous work in this laboratory by Mountjoy and Twomey utilised this method in the generation of α-diazoketones possessing contiguous *O*- and *S*-alkyl/benzyl moieties.[25,52] Overall, in this work, the unsymmetrical anhydride route proved a more reliable method to prepare the pyridine substituted α-diazoketones than the acid chloride approach for these substituted 3-pyridinepropanoic acids.

The internal α-diazoketones **134-139** derived from diazoethane were synthesised from their corresponding carboxylic acids **101-106** (**Scheme 2.58**) using the unsymmetrical anhydride procedure with ethyl chloroformate in low yield (**Table 2.9**). Despite the low yields, this approach reliably provided samples of the α-diazoketones each time it was attempted, in contrast to the acid chloride route. While this is a reproducible and reliable method to prepare pyridine-containing α-diazoketones, the yields were typically low. The corresponding ethyl esters **81**, **93** and **99** was observed as a significant side product in most cases and these were isolated in the case of **134**, **135** and **138**. However, in later experiments recovery of the ethyl ester from the column was not undertaken. The purification of α-diazoketones **134-139** required repeated column chromatography in some cases, in order to isolate analytically pure samples for characterisation. Notably, the results obtained refer to single experiments and were not repeated during this work.



Scheme 2.58

Table 2.9 *Isolated yields, characteristic stretching frequencies and rotameric signals for α-diazoketones* ***135-139***

Entry	Acid	Diazo	Yield (%)[a]	ν_{CO}/ cm^{-1}	ν_{CNN}/ cm^{-1}	δ_H $CNC\underline{H}_3$[b] major rotamer	δ_H $CN_2C\underline{H}_3$[b] minor rotamer
1	2-Cl **101**	2-Cl **134**	6	1631	2078	1.94 ppm	2.08 ppm
2	6-Cl **102**	6-Cl **135**	13	1630	2079	1.94 ppm	2.06 ppm
3	2,6-Cl_2 **103**	2,6-Cl_2 **136**	4	1627	2068	1.94 ppm	2.07 ppm
4	2-Br **104**	2-Br **137**	30	1631	2078	1.94 ppm	2.08 ppm
5	2-F **105**	2-F **138**	7	1630	2075	1.94 ppm	2.07 ppm
6	2-OMe **106**	2-OMe **139**	23	1638	2073	1.93 ppm	–

[a] Isolated yield after column chromatography and in many cases compounds required repeated chromatography.
[b] ^{1}H NMR in $CDCl_3$ [(300 MHz for **136**, **137** and **139**) and (400 MHz for **134**, **135** and **138**)].

Similar to earlier work with α-diazoketones **25** and **63-65**, the presence of rotamers was clearly identified in ~9 : 1 ratio in ^{1}H NMR spectra of pyridine-containing α-diazoketones **134-138** (**Table 2.9**). The signal for the α-substituted methyl group, $CN_2C(1)\underline{H}_3$ was observed as a broad singlet at δ_H ~1.94 ppm, similar to the corresponding signal in the phenyl analogues (**Section 2.3.1.2.2**). Interestingly, the signal for the minor rotamer (δ_H ~2.06–2.08 ppm) was located further downfield with respect to the major rotamer for **134-138**, in contrast to α-diazoketone analogues, **25** and **63-64**, which displayed the opposite effect (see **Table 2.2**). It is also noteworthy that the signal for $C(4)\underline{H}_2$ was broadened in the ^{1}H NMR spectrum and the presence of a broad triplet as the minor rotamer signal (δ_H ~2.69–2.76 ppm) was located slightly upfield from the major rotamer signal (δ_H ~2.78–2.84 ppm) for compounds **134-138** (**Figure 2.25**). The isolated yields, characteristic ^{1}H NMR and infrared spectroscopic signals are summarised in **Table 2.9**.

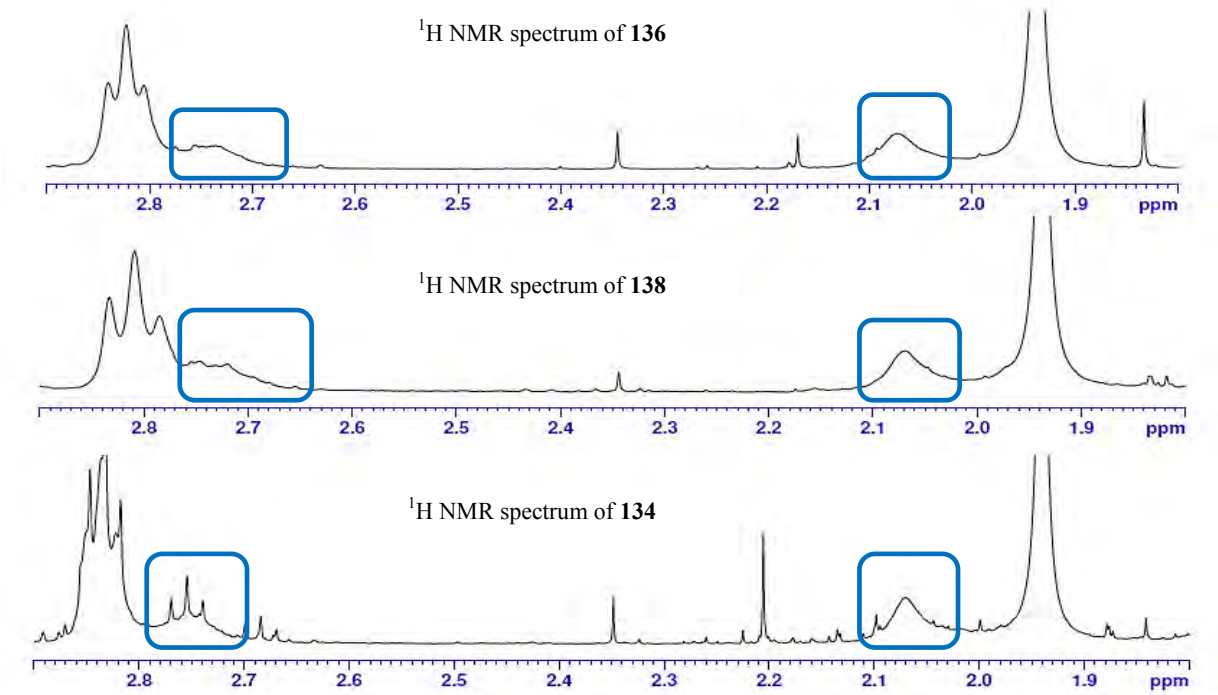
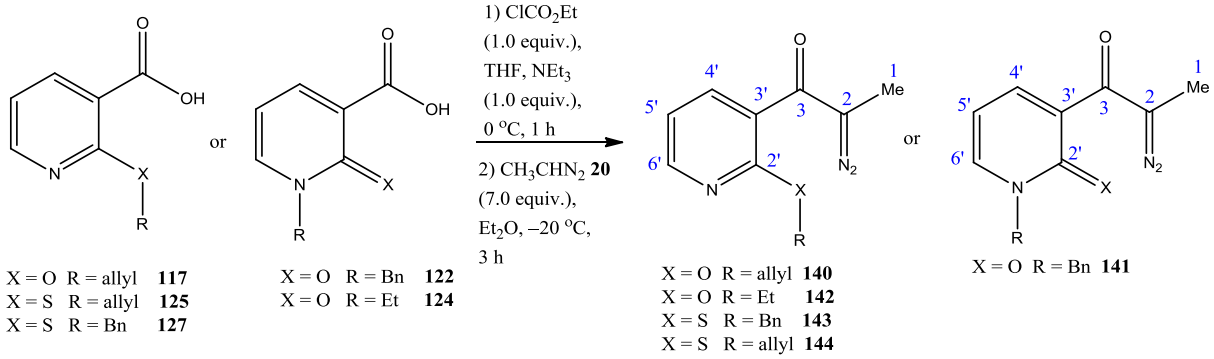


Figure 2.25: Partial ^{1}H NMR spectra (300, 400 and 500 MHz, $CDCl_3$) of 134 (500 MHz), 136 (400 MHz) and 138 (300 MHz) with identification of minor rotameric signals for C(4)$\underline{H_2}$

The unsymmetrical anhydride method was also successfully utilised in the formation of α-diazoketones derived from the *O*-, *N*- and *S*-substituted acids **117**, **122**, **124**, **125** and **127** (**Scheme 2.59**).[142] Similar to the synthesis of α-diazoketones **134-139** above, isolated yields of α-diazoketones **140-144** using this method were low and repeated chromatographic purification was required for some of the compounds. As summarised in **Table 2.10,** characteristic signals were seen in the infrared spectra for the diazo and carbonyl stretches, while in the ^{1}H NMR spectrum, a broad signal was seen for the methyl group adjacent to the diazo group at δ_H ~2.10 ppm. In this case, rotameric signals were not seen, however, signal broadening is indicative of restricted rotation.



Scheme 2.59

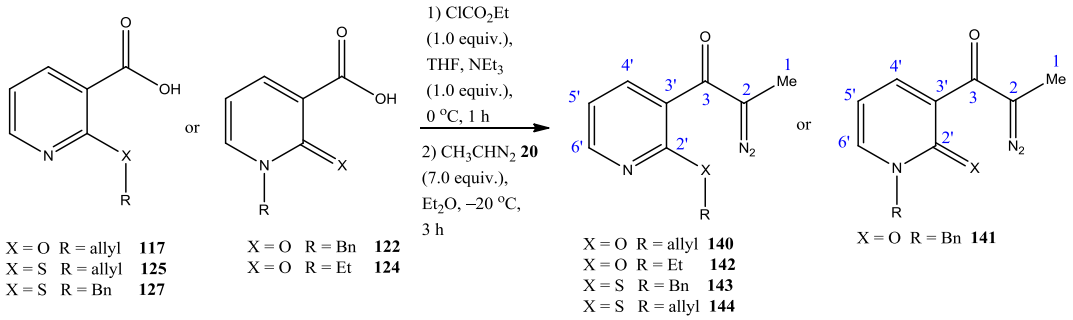
Interestingly, the α-diazoketones bearing both the pyridine and pyridone tautomers were accessible by this route and in each case were isolated as yellow oils which could be readily purified and handled. To the best of our knowledge, each of the α-diazoketones **140-144** is novel and we believe this is the first pyridone α-diazoketone of this type reported in the literature with the only comparable example being a pyridone α-diazocarbonyl compound **145** described by Padwa where the diazo moiety is tethered to a cyclic amine (**Scheme 2.60**).[143] The isolated yields and characteristic spectroscopic data are summarised below (**Table 2.10**). Four of the α-diazoketones prepared **140**, **141**, **143** and **144** were fully characterised and while ^{1}H NMR, infrared and mass spectrometry data were obtained for '*N*-ethyl' α-diazoketone **142** (see below), in this case ^{13}C NMR analysis was not obtained.

Comparison of spectroscopic signals for the α-diazoketones **141**, **142** and *N*-allyl derivative **207** synthesised later (see **Section 2.3.2.4**) indicates that while the *N*-ethyl acid **124** was used as starting material to prepare **142**, as determined by ^{1}H NMR spectroscopy and X-ray crystallography, it appears that the *O*-ethyl α-diazoketone is the product generated from the acylation. Characteristic stretches for the carbonyl moiety of the pyridones are observed at ν_{max} 1654 cm^{-1} for **141** and **207**, while the carbonyl band is seen at ν_{max} 1611 cm^{-1} in the case of **142**. In addition, ^{1}H NMR spectroscopy illustrates that the atom connectivity of **142** is different than obtained for pyridones **141** and **207**, with the distinguishing feature the signal for C(5')H, seen at δ_H 6.24 and 6.28 ppm for **141** and **207** respectively, while the corresponding signal is identified at δ_H 7.32 ppm for α-diazoketone **142**. Furthermore, ^{1}H NMR signals for the analogous 2-ethoxynicotinic acid have been reported at δ_H 4.69, 7.13, 8.37 and 8.48 ppm,[150] which is comparable to signals for **142** seen at δ_H 4.32, 7.32, 7.86 and 8.46 ppm.

Thus, the generation of the *O*-ethyl derivative **142** appears to be an anomalous result by comparison with formation of *N*-alkylated derivatives only for α-diazoketones **141** and **207**. Formation of this tautomer could possibly be due the length of time the acid **124** was stored in the freezer prior to α-diazoketone formation (~2 months), although an appropriate explanation is not presented at this time and this assignment of the *O*-ethyl derivative is tentative. This reaction needs to be repeated to verify if this is a once-off transformation and ^{13}C NMR analysis of the α-diazoketone product would presumably aid assignment through comparison with signals reported for *N*-alkylated analogues **141** and **207**.

While there is precedent for interconversion of *O*-alkyl to *N*-alkyl tautomers of pyridines and pyridones, this has been achieved by forceful conditions involving microwave irradiation,[151] flash vacuum pyrolysis[152] and iridium catalysis.[153] Interestingly, there is a report for the interconversion of an *N*-alkylated derivative to the *O*-alkylated tautomer, which utilised tin(IV) chloride in the reaction.[154]

Table 2.10 *Isolated yields and characteristic infrared stretching frequencies for α-diazoketones* ***140-144***



X = O R = allyl **117**
X = S R = allyl **125**
X = S R = Bn **127**

X = O R = Bn **122**
X = O R = Et **124**

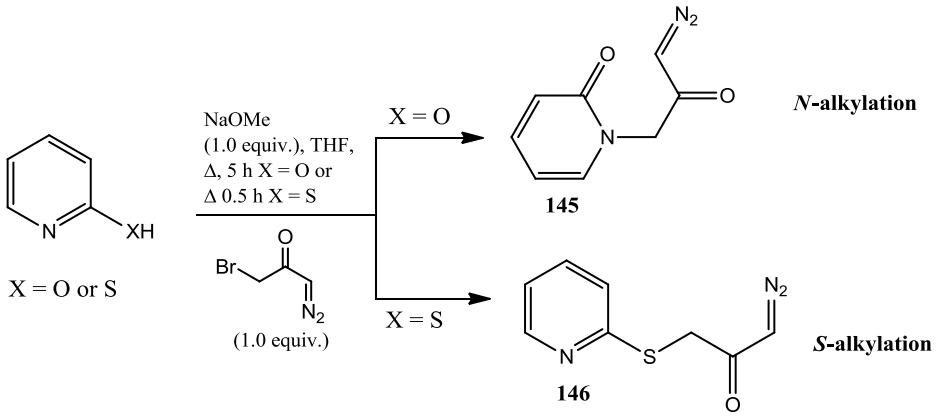
X = O R = allyl **140**
X = O R = Et **142**
X = S R = Bn **143**
X = S R = allyl **144**

X = O R = Bn **141**

Entry	Acid	R	*O/S*-alkyl diazo	*N*-alkyl diazo	Yield (%)[a]	ν_{CO}/ cm^{-1}	ν_{CNN}/ cm^{-1}	δ_H $CN_2C\underline{H}_3$[b]
1	**117**	allyl	**140**	–	30	1604	2078	2.11 ppm
2	**122**	Bn	–	**141**	24	1654	2081	2.08 ppm
3	**124**	Et	**142**[c]	–	7	1611	2084	2.09 ppm
4	**127**	Bn	**143**	–	23	1604	2078	2.07 ppm
5	**125**	allyl	**144**	–	4	1607	2080	2.10 ppm

[a] Isolated yield after column chromatography and in some cases compounds required repeated chromatography.
[b] ^{1}H NMR in $CDCl_3$ and 400 MHz.
[c] Tentatively assigned as *O*-ethyl α-diazoketone through comparison of spectroscopic signals for *N*-alkyl α-diazoketones **141** and **207** (**Section 2.3.2.4**).

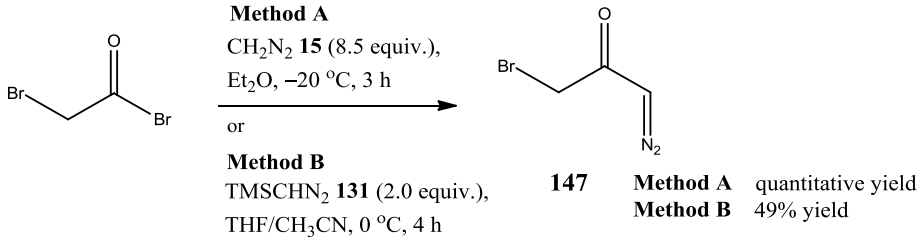
In 1993, Padwa and co-workers reported an alternative approach to prepare pyridine α-diazoketones synthesised by reaction of an α-bromo-α'-diazoketone with a hydroxyl or thiol substituted pyridine (**Scheme 2.60**),[143] leading to heteroatomic linkers in the side-chain containing the diazo moiety (see **Section 1.5.3.4.4**). Interestingly, Padwa reported alkylation at the nitrogen using 2-hydroxypyridine to generate **145** and alkylation at the sulfur using 2-mercaptopyridine to afford **146**,[143] which is in good agreement with our efforts in alkylation reactions of analogous 2-hydroxynicotinic acid **118** and 2-mercaptonicotinic acid **120** (see **Section 2.3.1.4**). This methodology was followed in this project to prepare 2-substituted substrate **146**, previously synthesised by Padwa,[143] as well as synthesis of the novel 4-substituted pyridine analogue **150**.



Scheme 2.60: Preparation of pyridine and 2-pyridone-containing α-diazoketones[143]

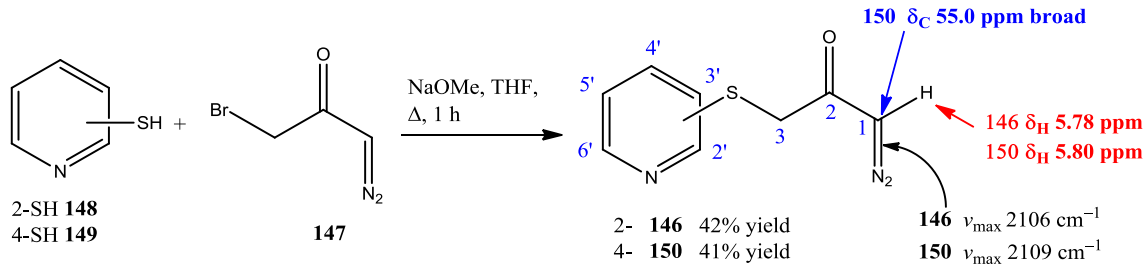
The first step in this strategy was the formation of an α-bromo-α'-diazoketone by reacting bromoacetyl bromide with diazomethane **15**, as carried out by Padwa,[143] or the commercially available alternative $TMSCHN_2$ **131**. While use of $TMSCHN_2$ has primarily focused on methylation reactions,[146-148] acylation of this compound to prepare terminal α-diazoketones has been demonstrated by Dolenc[142] *via* unsymmetrical anhydrides, while Makhey[141] and O'Neill[12] have employed acid chloride intermediates respectively.

Following Padwa's method,[143] generation of diazomethane **15** from Diazald® and reaction with bromoacetyl bromide afforded 1-bromo-3-diazopropan-2-one **147** in quantitative yield after chromatography (**Scheme 2.61**), although a higher number of equivalents were used in this work than employed by Padwa (~8.5 equiv. *cf.* 3.0 equiv.). Using the $TMSCHN_2$ instead, 1-bromo-3-diazopropan-2-one **147** was isolated in 49% yield following purification (**Scheme 2.61**). Spectroscopic data for α-bromo-α'-diazoketone **147** were consistent with values described by Padwa.[143] As Diazald® is no longer commercially available, method B using $TMSCHN_2$ **131** was the more practical approach to prepare compound **147**. While synthesis of compound **147** has previously been reported using diazomethane **15**,[143,155-158] this is the first example of its preparation *via* acylation of $TMSCHN_2$.



Scheme 2.61

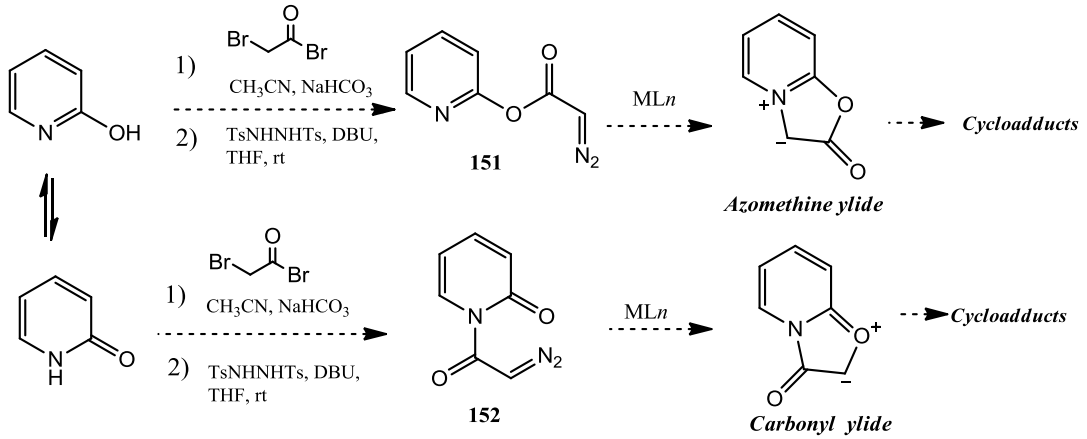
Preparation of the α-diazoketones involved addition of a THF suspension of sodium methoxide and 2- or 4-mercaptopyridine **148** or **149** to a tetrahydrofuran solution of 1-bromo-3-diazopropan-2-one **147**. The reaction mixture was heated under reflux for 1 h and completion of the reaction was determined by TLC analysis and infrared spectroscopy. Purification by column chromatography furnished the terminal 2- and 4-substituted pyridine α-diazoketones **146** and **150** in 42% and 41% isolated yield respectively as yellow oils (**Scheme 2.62**). Since **146** was previously synthesised by Padwa,[143] only infrared and ^1H NMR spectroscopic analysis was carried out on this compound, whereas the novel α-diazoketone **150** was fully characterised. The spectroscopic characteristics for α-diazoketone **146** were consistent with those previously described by Padwa.[143] The terminal α-diazoketones had a characteristic absorption in the 2100–2110 cm^{-1} region of the infrared spectrum, observed at ν_{max} 2106 cm^{-1} for **146** and ν_{max} 2109 cm^{-1} for **150**, while the ^1H NMR spectrum displayed a broad singlet at δ_H 5.78 ppm for **146** and δ_H 5.80 ppm for **150**, accounting for the α-proton, C<u>H</u>N_2 (**Scheme 2.63**). In the ^{13}C NMR spectrum of **150**, a broad peak was observed at δ_C 55.0 ppm, corresponding to the carbon attached to the diazo moiety. In the high resolution mass spectrometry of **150**, the molecular ion was identified without loss of nitrogen unlike most of the previous α-diazocarbonyl substrates investigated.



Scheme 2.62: Characteristic signals for 146 and 150 from ^{1}H NMR (300 MHz, $CDCl_3$) and infrared spectroscopy

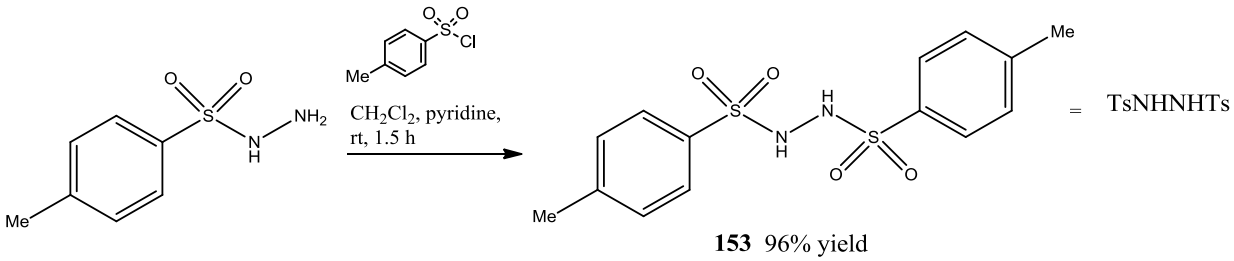
While α-diazoketones **146** and **150** were successfully prepared and characterised, their reactivity was not explored during this work, whereas Padwa has described 1,3-dipole formation from **146**.[143] It is possible that the route could be expanded through use of β- or γ-bromo-α-diazoketones, although this has not been reported by Padwa. Further variation could involve employing different dipolarophiles than previously reported by Padwa for the 1,3-dipolar cycloaddition, *e.g.* 4-phenyl-1,2-4-triazole-3,5-dione (PTAD) adducts.[143]

Final efforts to generate α-diazoketones of interest *via* acylation of diazoalkanes involved formation of α-diazoacetates using the procedure described by Fukuyama and co-workers in 2007 (see **Section 1.2.1.7**).[144] In their work, this method allowed the synthesis of a range of α-diazoacetates from the corresponding alcohols in good to high yields. While a range of phenyl, carbocyclic and aliphatic α-diazoacetates were prepared by Fukuyama using this method, no heterocyclic α-diazoacetates were investigated in any of Fukuyama's studies. Building on Fukuyama's work,[144] the use of 2- and 3-hydroxypyridines as substrates potentially allows the construction of novel α-diazoketones of type **151** or **152**. Carbenoid-mediated reactions of these compounds could be envisaged to lead to the assembly of carbonyl and azomethine ylides, which may undergo intermolecular 1,3-dipolar cycloaddition reactions (**Scheme 2.63**).



Scheme 2.63: Reaction pathways using 2-hydroxypyridine and 2-pyridone substrates

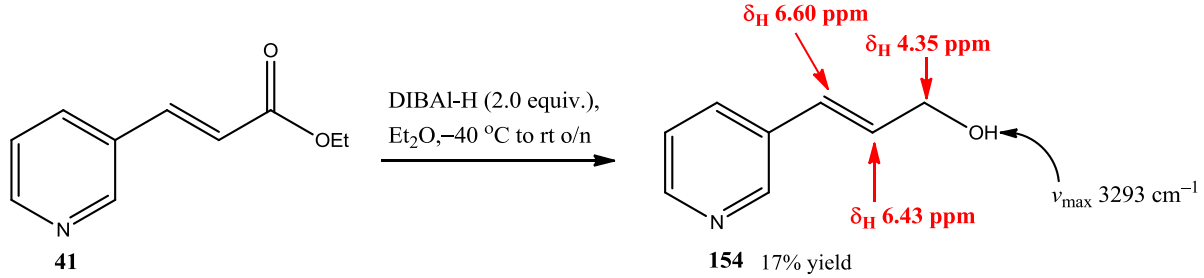
Preparation of *N*,*N*′-ditosylhydrazine **153** was carried out following Fukuyama's procedure using *p*-toluenesulfonylhydrazide and *p*-toluenesulfonyl chloride in pyridine (**Scheme 2.64**).[144] Compound **153** was synthesised in 96% yield following a recrystallisation from hot methanol and was deemed sufficiently pure to be brought forward without further purification. While analysis by infrared spectroscopy was in agreement with values described by Fukuyama,[144] there was a significant discrepancy in the ^{1}H NMR spectroscopic data described by Fukuyama and those obtained in this work, even though the same solvent (DMSO-d_6) was used in the analysis. However, the values obtained in this work were in excellent agreement with data disclosed by Grehn and co-workers for **153** using DMSO-d_6 as solvent.[159] As the values described by Fukuyama[144] differ by ~0.8 ppm for all the signals from values in this work and by Grehn,[159] it is likely than an incorrect calibration is responsible for the discrepancy of the signals observed in the ^{1}H NMR spectrum.



153 96% yield

Scheme 2.64

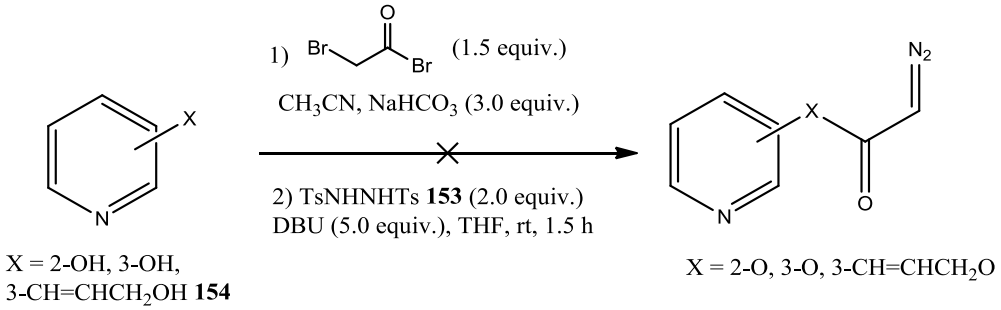
In this work, preparation of α-diazoacetates was attempted from commercially available 2-hydroxypyridine and 3-hydroxypyridine, as well as (*E*)-2-(pyridin-3-yl)ethanol **154**, which was prepared from reduction of the corresponding ethyl acrylate ester **41** (**Scheme 2.65**). The reduction was accomplished following the procedure outlined by Helmchen,[160] using diisobutylaluminium hydride (DIBAl-H) and ether resulting in synthesis of the alcohol **154** as an orange oil in 17% yield. Infrared spectroscopy of **154** was consistent with values reported in the literature, ν_{max} 3293, 2852, 1657 and 1591 cm^{-1} *cf.* ν_{max} 3300, 2860, 1655 and 1590 cm^{-1}.[160] Characteristic ^{1}H NMR spectroscopic signals included the appearance of the methylene group at δ_H 4.35 ppm as a doublet of doublets (*J* 5.2, 1.2 Hz), as well as identification of the alkene peaks at δ_H 6.43 and 6.60 ppm. These values were in accordance with those described by Helmchen (δ_H 4.34, 6.41, 6.59 ppm).[160]



41 **154** 17% yield

Scheme 2.65

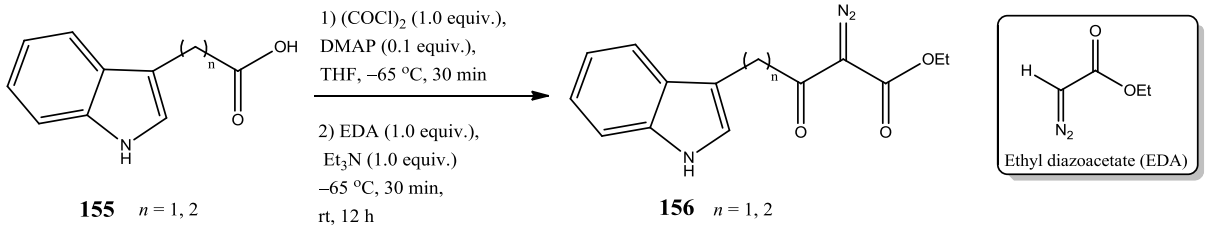
For each of the substrates 2-hydroxypyridine, 3-hydroxypyridine and 3-pyridylallyl alcohol **154**, Fukuyama's protocol was explored (**Scheme 2.66**), reacting initially with bromoacetyl bromide in the presence of $NaHCO_3$ followed by addition of *N*,*N*′-ditosylhydrazine **153** and DBU. However, there was no evidence for the formation of an α-diazoacetate in any of these experiments, which suggests the pyridine ring is incompatible with these reaction conditions. In the context of Padwa's results in the alkylation of 2-hydroxypyridine (**Scheme 2.60**),[143] it is likely that the challenge lies in the second step involving reaction of α-bromoacetate with *N*,*N*′-ditosylhydrazine **153** and DBU. In retrospect, repeating Fukuyama's procedure with one of their substrates in advance of attempting it with the pyridine substrates might have proved useful. This approach has been used successfully in **Chapter 3**, **Section 3.3.2.2** to prepare α-diazoacetates from their corresponding allylic alcohols.



Scheme 2.66

2.3.1.5.2 Preparation of α-diazo-β-ketoesters via *acylation of diazoalkanes*

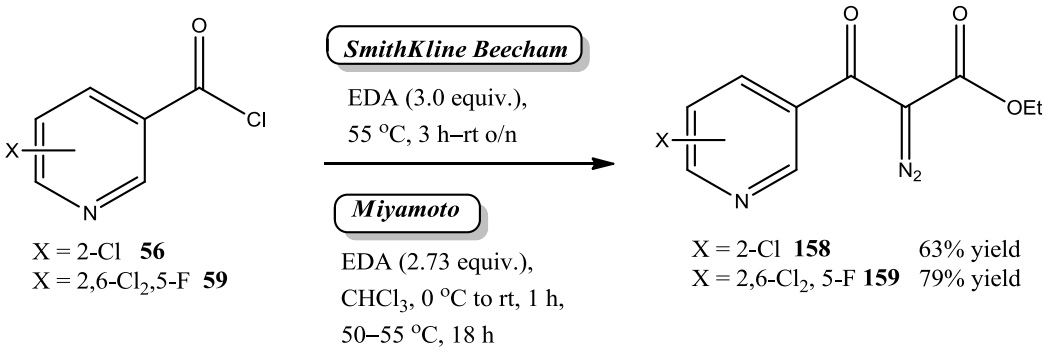
Cuevas-Yañez and co-workers have described the construction of α-diazo-β-ketoesters in one step, as opposed to the more conventional route of initial formation of the β-ketoester and subsequent diazo transfer methodology (**Scheme 2.67**).[161] This work was carried out by reaction of an indole carboxylic acid **155** with oxalyl chloride in the presence of DMAP to generate the acid chloride, which was later reacted with commercially available ethyl diazoacetate and triethylamine at −65 °C to afford the α-diazo-β-ketoesters **156**.



Scheme 2.67

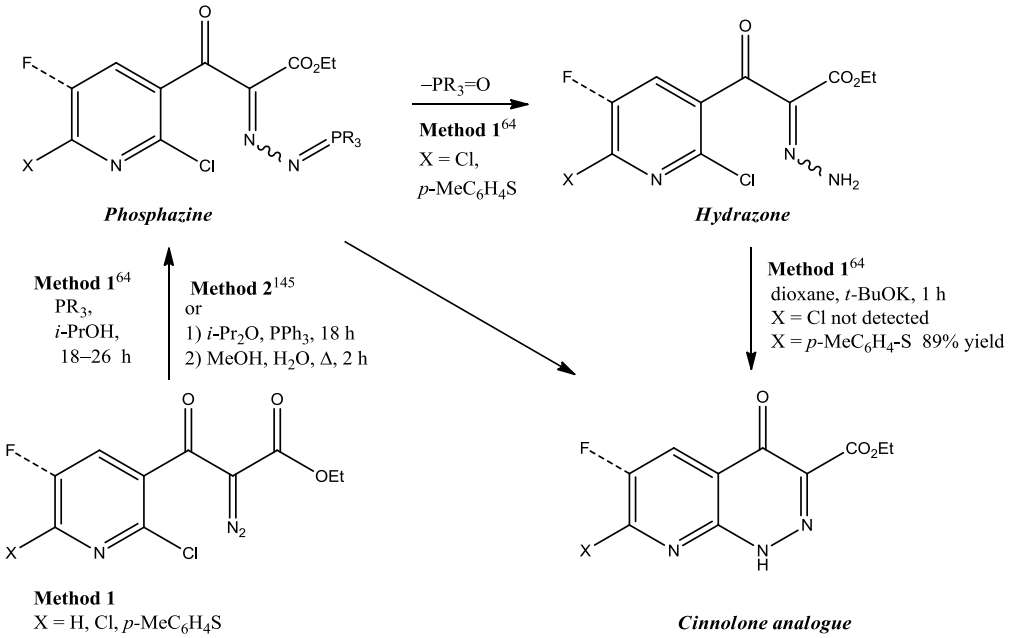
As halogenated 3-nicotinoyl chlorides were efficiently prepared earlier in this work, it was decided to use each of the acid chlorides **56** and **59-60** as substrates for this streamlined method to prepare the α-diazo-β-ketoesters. Miyamoto has previously reported the generation of pyridine-containing α-diazo-β-ketoester **159** using this one-step operation from the acid

chloride,[64] while workers at SmithKline Beecham have also exploited this strategy in the synthesis of **158** (**Scheme 2.68**).[145]



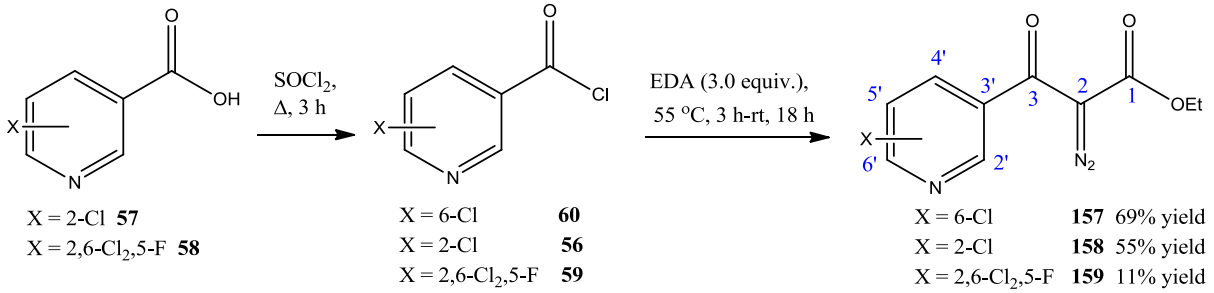
Scheme 2.68

These substrates were developed for the same purpose by both Miyamoto[64] and SmithKline Beecham,[145] methods 1 and 2 respectively (**Scheme 2.69**). In both cases, α-diazo-β-ketoester **158** or **159** was subsequently reacted with a triarylphosphine to generate a reactive triarylphosphazine, which could hydrolyse to the corresponding hydrazone or undergo cyclisation to generate the Cinnolone analogue target. In Miyamoto's work, direct cyclisation of the triarylphosphine and sequential reaction of the hydrazone were both observed for *p*-tolylthio substrate, whereas for the 6-chloro derivative **159**, generation of the Cinnolone analogue was only achieved *via* the direct route. SmithKline Beecham reported the reductive cyclisation of the triphenylphosphazine intermediate to provide the Cinnolone analogue. These target compounds are similar to the core structures of antibacterials norfloxacin[162] and enoxacin,[163] as well as related analogues developed by Miyamoto.[164,165]



Scheme 2.69: Work by both Miyamoto[64] and SmithKline Beecham[145]

The α-diazo-β-ketoesters **157-159** were prepared in this work following the procedure outlined by SmithKline Beecham reacting acid chlorides **56** and **59-60** with ethyl diazoacetate (**Scheme 2.70**). The reaction conditions involved heating of the acid chloride (1.0 equiv.) and ethyl diazoacetate (3.0 equiv.) together at 55 °C for 3 h, followed by stirring at room temperature for 18 h.[145] Purification by column chromatography provided each of the three α-diazo-β-ketoesters **157-159** as bright yellow oils, which later solidified on storage. These compounds were prepared in good yields for **157** and **158**, but much lower in the case of **159**. SmithKline Beecham[145] and Miyamoto[64] have previously reported preparation of **158** and **159** respectively *via* this one-step protocol, therefore, analysis of **158** and **159** consisted of melting point, ^{1}H NMR and infrared spectroscopy only. Spectroscopic data for **158** and **159** were consistent with previously reported data.[64,145] As **157** is the only novel compound of the three, further characterisation including melting point, infrared, ^{1}H and ^{13}C NMR spectroscopy, nominal and high resolution mass spectrometry were undertaken for this compound. The samples of α-diazo-β-ketoester **157-159** isolated were easy to handle and stable, and could be stored up to ~3 months in the freezer without degradation.



Scheme 2.70

During this work, following growth of a crystal from a sample of **159** in $CDCl_3$, an X-ray crystal structure of compound **159** was also obtained (**Figure 2.25**). The dihedral angle between the diazo and carbonyl groups around the C(1)=O and C(2)N_2 bond in **159** is 170°, while similarly, the corresponding dihedral angle between the C(3)=O and C(2)N_2 bond is −7.7°. This once again illustrates a minor deviation from planarity of the diazo and carbonyl groups due to packing constraints. In addition, the pyridyl ring and diazo groups also show a divergence from planarity as evidenced by the C3'-C3-C2-N5 torsion angle (−18.02°). Also, the pyridyl ring and the adjacent carbonyl group are out of plane (−57.47°). Two halogen bonds arising from O···Cl interactions (both 3.00 Å) branch out in opposite directions in the crystal structure of α-diazo-β-ketoester **159** (**Figure 2.26**).

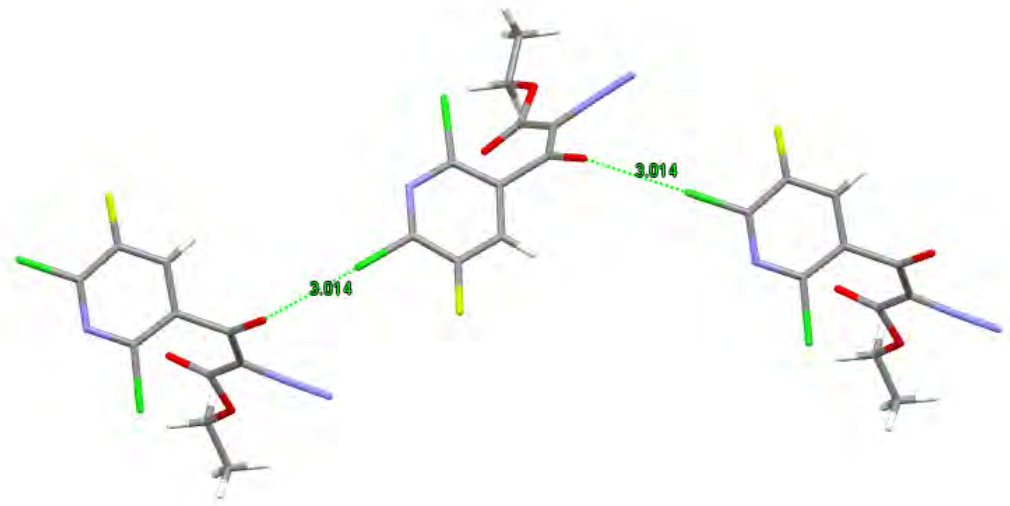
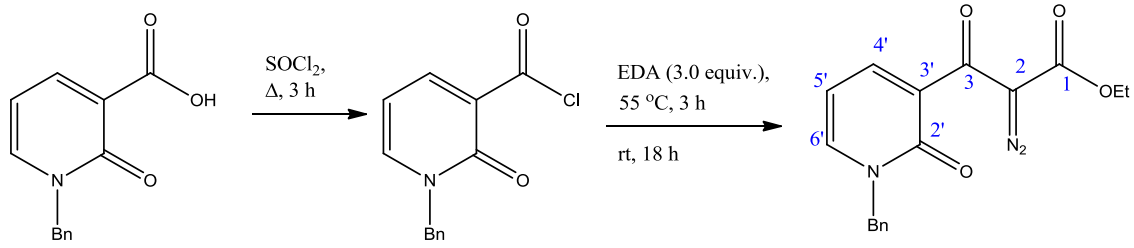


Figure 2.26: X-ray crystal structure of 159

The *N*-benzyl acid **122** was converted to the corresponding acid chloride **160** following a method described by Masu by heating acid **122**, toluene, thionyl chloride under reflux for 3 h (**Scheme 2.71**).[126] Although preparation of acid chloride **160** has been reported by both Masu[126] and Oxford Glycosciences,[166] no spectroscopic analysis was described for this compound. Acid chloride **160** was isolated in 90% crude yield as a yellow/orange solid with a characteristic infrared absorption ascribed to the acid chloride at ν_{max} 1772 cm^{-1}. Compound **160** was used for the preparation of the novel *N*-benzyl α-diazo-β-ketoester **161** following the method originally described by SmithKline Beecham for synthesis of **158** and employed above.[145] The α-diazo-β-ketoester **161** was obtained as a brown oil in 23% yield after purification by column chromatography. The isolation of **161** as a brown oil was in contrast to other α-diazo-β-ketoesters **157-159** which were initially isolated as bright yellow oils which solidified on storage. To the best of our knowledge, this is the first report of preparation of a pyridone α-diazo-β-ketoester following this route.



Scheme 2.71

In each case, these α-diazo-β-keotesters were synthesised just once without optimisation. The isolated yields, melting points and characteristic infrared stretching frequencies obtained for α-diazo-β-ketoesters **157-159** and **161** are summarised below (**Table 2.11**).

Table 2.11 *Isolated yields, melting point and characteristic infrared stretching frequencies for α-diazo-β-ketoesters* ***156-158*** *and* ***160***

Entry	Acid chloride	Diazoester pyridine	Diazoester pyridone	ν_{CO}/ cm^{-1}	ν_{CNN}/ cm^{-1}	m.p. (°C)	Yield (%)[a]
1	**60**	**157**	–	1721 & 1628	2150	38–41	69
2	**56**	**158**	–	1723 & 1636	2152	36–38	55
3	**59**	**159**	–	1723 & 1639	2148	75–78	11[b]
4	**160**	–	**161**	1723 & 1655	2133	–	23

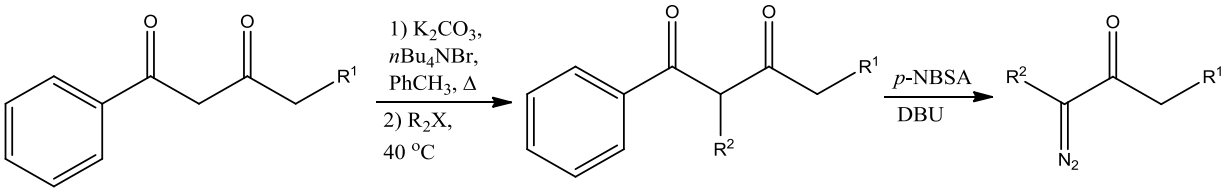
[a] Isolated yield after column chromatography.
[b] Sample not isolated cleanly and contained a significant amount of co-eluting ethyl diazoacetate.

2.3.2 Preparation of α-diazoketones involving diazo transfer methodology

2.3.2.1 Background

An alternative synthetic strategy for formation of α-diazoketones has been developed within the Maguire research group by Dr. Alan Ford involving a three-step synthesis.[167]

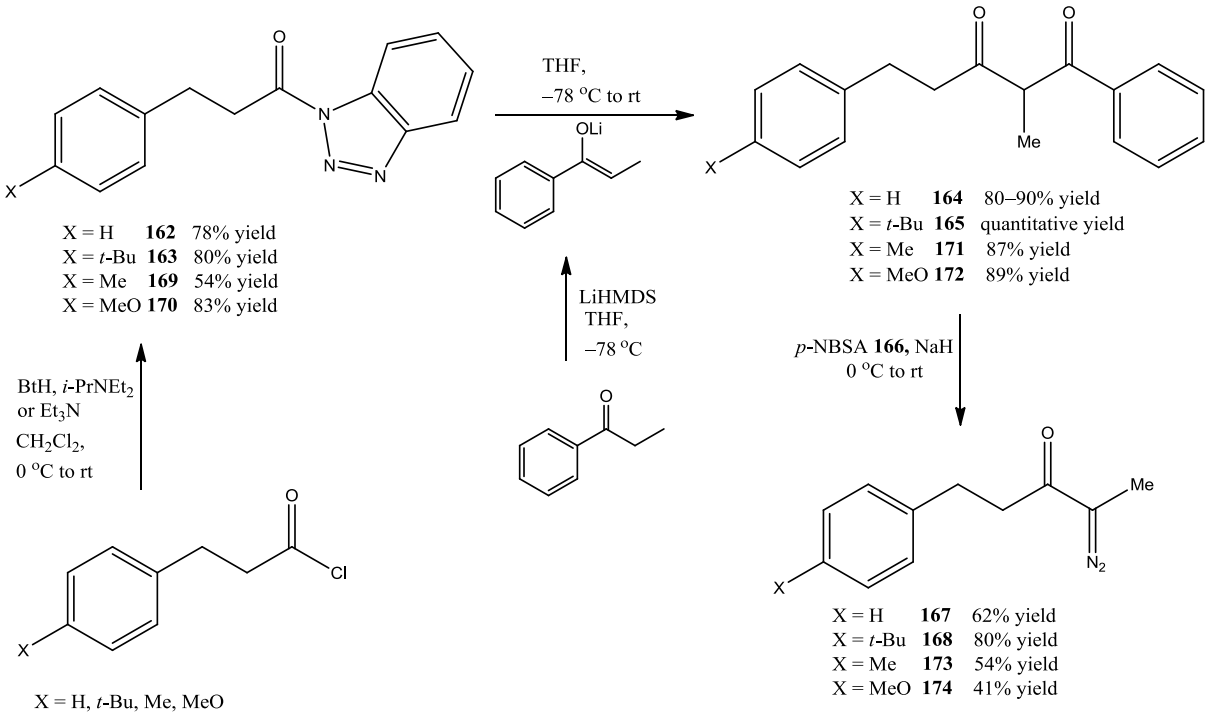
Taber and co-workers have reported an effective procedure for concomitant diazo transfer and debenzoylation in the generation of unsymmetrical α-diazoketones using *p*-nitrobenzenesulfonyl azide (*p*-NBSA) as diazo transfer reagent and DBU as the base.[168] This methodology is illustrated below (**Scheme 2.72**).



Scheme 2.72: Taber diazo transfer methodology for unsymmetrical α-diazoketones[168]

With this in mind, Ford proposed that various acid chlorides or carboxylic acids could be converted to the corresponding acylbenzotriazoles and subsequently transformed to β-diketones, serving as substrates for the Taber diazo transfer/debenzoylation methodology. This procedure enables formation of unsymmetrical α-diazoketones avoiding the use of hazardous diazoethane **20**. Employing this strategy, Ford prepared acylbenzotriazoles **162**, **163** and β-diketones **164**, **165** as precursors towards the successful synthesis of α-diazoketones **167**, **168** (**Scheme 2.73**).[167] Interestingly, Ford identified that use of sodium hydride as base with *p*-NBSA **166** as diazo transfer reagent gave superior yields to those obtained under the conditions described by Taber involving DBU and *p*-NBSA.[168] Furthermore, generation of acylbenzotriazole directly from the carboxylic acids is possible.

McDowell subsequently applied Ford's optimised procedure in the synthesis of α-diazoketones.[7] The requisite acylbenzotriazoles **169**, **170** and 1,3-diketone **171**, **172** precursors were generated in excellent yields and were successfully converted to the unsymmetrical α-diazoketones **173** and **174**. This work illustrates the reproducibility of this methodology, as well as an extension of the substrate range (**Scheme 2.73**).



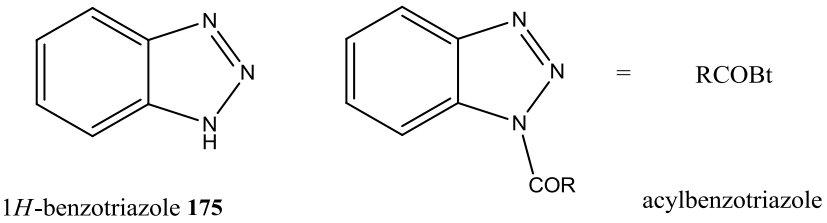
Scheme 2.73: Syntheses by Ford[167] and McDowell[7]

In a broad sense, the acylbenzotriazole can be viewed as a "tame" acyl halide substitute, as described by Katritzky,[169] with the benzotriazole moiety behaving as an effective activating group which can be easily displaced. These compounds are more stable and easier to work with than analogous acylating agents such as acid chlorides.[56] Fortified with this knowledge, a route towards unsymmetrical α-diazoketones using acylbenzotriazoles, circumventing the use of acid chlorides was next explored with the pyridine substrates in this work.

2.3.2.2 Preparation of acylbenzotriazoles

Since the early 1960s, when Staab carried out seminal work on acylimidazoles,[170,171] the use of acylazole compounds as acylating agents has permeated into the arsenal of synthetic organic chemists. Subsequently, Katritzky investigated acylbenzotriazoles to effect acylation and since work in the late 1980s became the preeminent figure with respect to almost all aspects of benzotriazole chemistry.[172-174] Acylbenzotriazoles possess many traits which make them synthetically advantageous building blocks, namely they are inexpensive, odourless, non-toxic, crystalline, non-volatile, have a long shelf life as well being compatible with chiral starting materials leading to retention of chirality.[175] The synthetic applications of these compounds range from benzotriazole-mediated acylation (N-,[176-179] C-,[180-183] S-[184] and O-

acylation),[185] imidoylation,[186,187] thioacetylation,[188,189] sulfonation[190] and various alkylation reactions leading to ethers[191-193] and thioethers.[194,195] A general example of acylbenzotriazoles, as well as 1*H*-benzotriazole **175** is displayed (**Figure 2.27**).



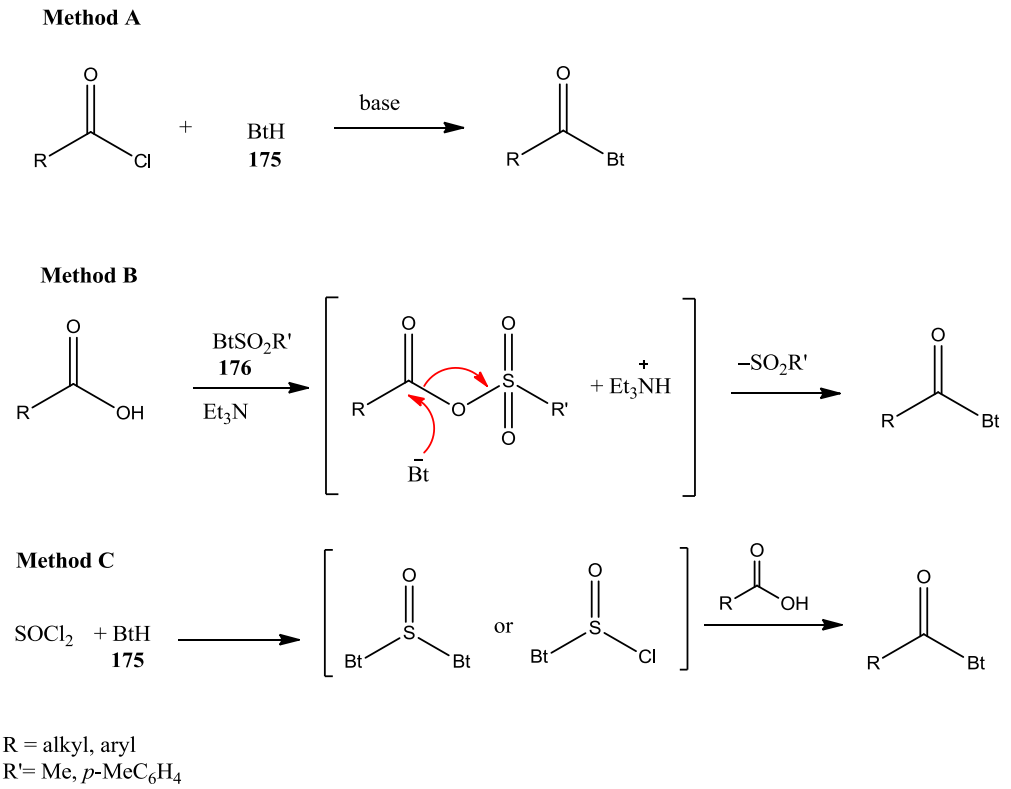
1*H*-benzotriazole **175** acylbenzotriazole

Figure 2.27

There are three methods commonly used in the preparation of acylbenzotriazoles, all of which start with the corresponding carboxylic acid (**Scheme 2.74**). Method A involves generation of an acid chloride from the carboxylic acid followed by reaction with 1*H*-benzotriazole **175** in the presence of a base to afford the acylbenzotriazole.[167] The two remaining methods completely avoid formation of the acid chloride, making them compatible with a broader range of substrates.

The first of the newer procedures (Method B) involves a sulfonyl benzotriazole **176** as a "counter attack" reagent, which in the presence of triethylamine, generates the desired acylbenzotriazole in one-step from the carboxylic acid.[56] It has been suggested the acylbenzotriazole results from initial formation of a mixed carboxylic sulfonic anhydride which subsequently undergoes an acylation reaction with the newly-liberated benzotriazole anion (**Scheme 2.74**). The major advantage of this method lies in its compatibility with heterocyclic carboxylic acids such as pyridine carboxylic acids. In the case of these substrates, many of the analogous acid chlorides are unstable, difficult to prepare or isolate and have not been reported.[56]

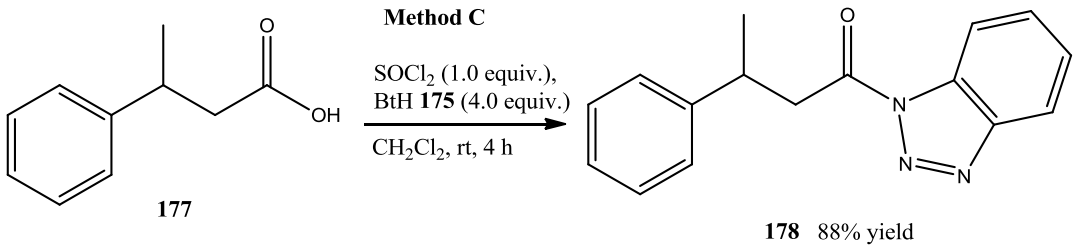
Katritzky later published a one-pot procedure (Method C) using carboxylic acid (1 equiv.), thionyl chloride (1 equiv.) and benzotriazole (4 equiv.) to provide the respective acylbenzotriazoles in high yield (**Scheme 2.74**).[196]



Scheme 2.74: Methods for the preparation of *N*-acylbenzotriazoles (Scheme from Katritzky)[197]

Based on Ford's results,[167] use of this methodology was explored as an alternative route towards the preparation of pyridine substituted α-diazoketones. These compounds have been synthesised earlier in this project in low yields *via* acylation of diazoalkanes using an unsymmetrical anhydride approach (see **Section 2.3.1.5.1**). In the course of this work, all three methods were used to construct the acylbenzotriazoles and in the case of each compound, this will be referred to as Method A–C, as described above.

Initial work focused on preparing a standard *N*-acylbenzotriazole substrate to become familiar with the techniques for the first and subsequent steps in the synthesis. The commercially available 3-phenylbutanoic acid **177** was the first substrate investigated using the one-pot method (Method C), developed by Katritzky (**Scheme 2.75**).[196] This process involved 3-phenylbutanoic acid **177**, 1*H*-benzotriazole **175** and thionyl chloride at room temperature, with the crude acylbenzotriazole isolated after basic workup of the reaction mixture. Purification by column chromatography afforded the pure 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-phenylbutan-1-one **178** as a white solid in 88% yield. Since all of the acylbenzotriazoles apart from compound **179** were novel, complete characterisation was undertaken.



Scheme 2.75

The ^{1}H NMR spectrum of **178** is shown below (**Figure 2.28**) and the characteristic benzotriazole protons are observed as distinctive doublets of doublets of doublets at δ_H 7.48 and 7.61 ppm (*J* 8.4, 7.2, 0.8 Hz) for C(5)H and C(6)H, while doublets with further unresolved splitting (δ_H 8.09 and 8.24 ppm, *J* 8.4 Hz) are ascribed to C(4)H and C(7)H. The doublets of doublets of doublets are located further upfield than the unresolved doublets across the range of acylbenzotriazoles investigated. Analysis of **178** by ^{13}C NMR spectroscopy also highlighted characteristic signals for the acylbenzotriazole at δ_C 131.1 and 145–146 ppm, attributed to C(7)a and C(3)a respectively (**Figure 2.29**). The signals for the quaternary carbons, C(7)a and C(3)a are consistent across all of the acylbenzotriazoles synthesised in this work.

Notably, this is the first time in our lab where the acylbenzotriazoles were synthesised directly from the carboxylic acids using Methods B and C, avoiding the use of acid chloride intermediates or use of DCC coupling reagent as previously carried out by Ford.[167]

The general numbering scheme for the pyridine acylbenzotriazoles prepared is shown below (**Figure 2.28**).

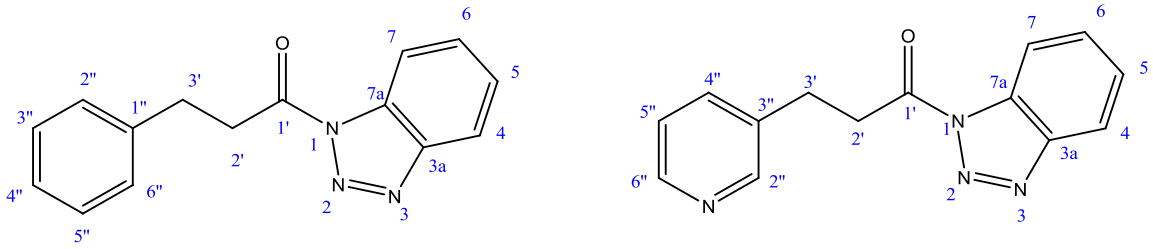


Figure 2.28: Sample numbering scheme of phenyl and pyridine acylbenzotriazoles

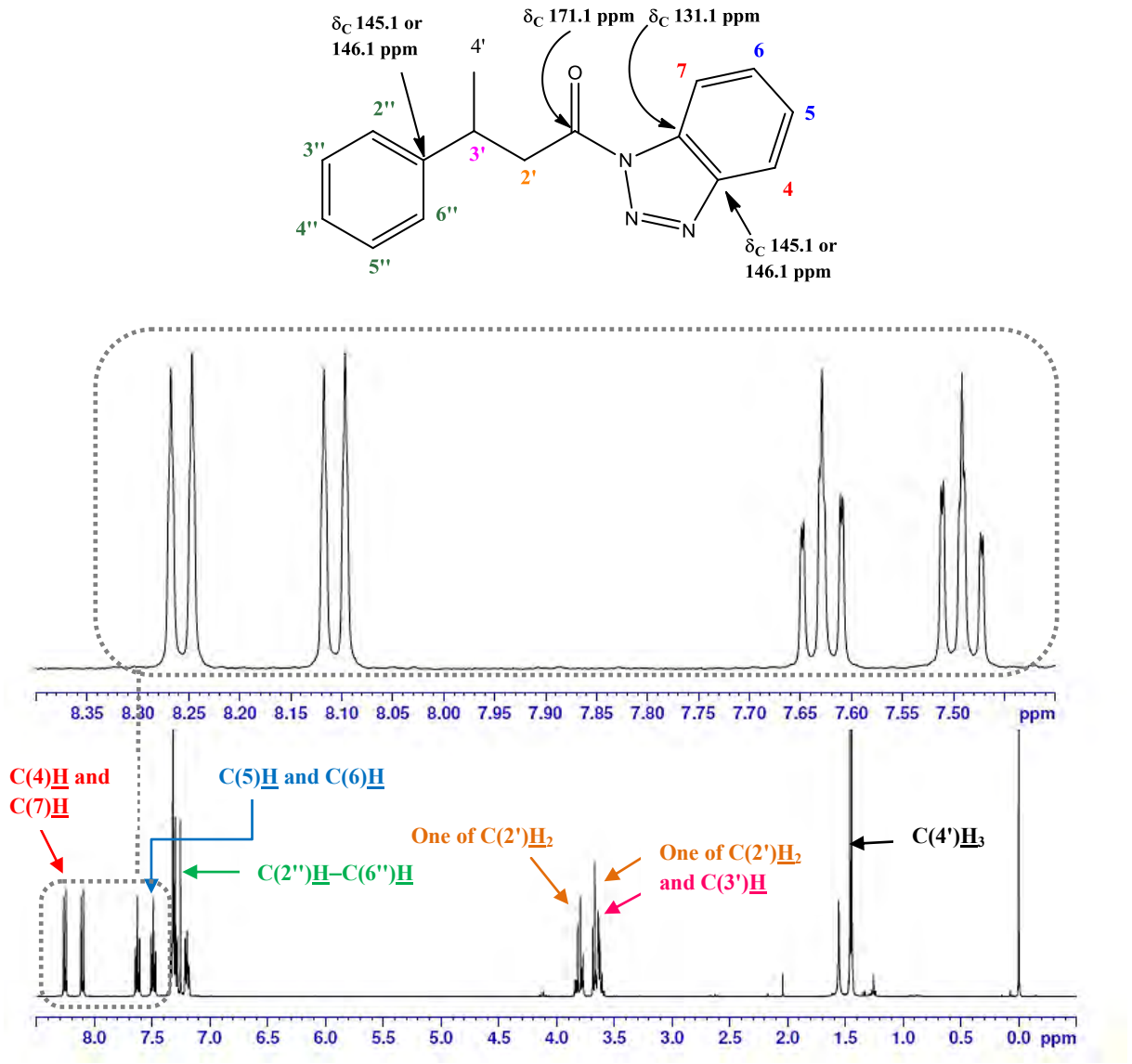
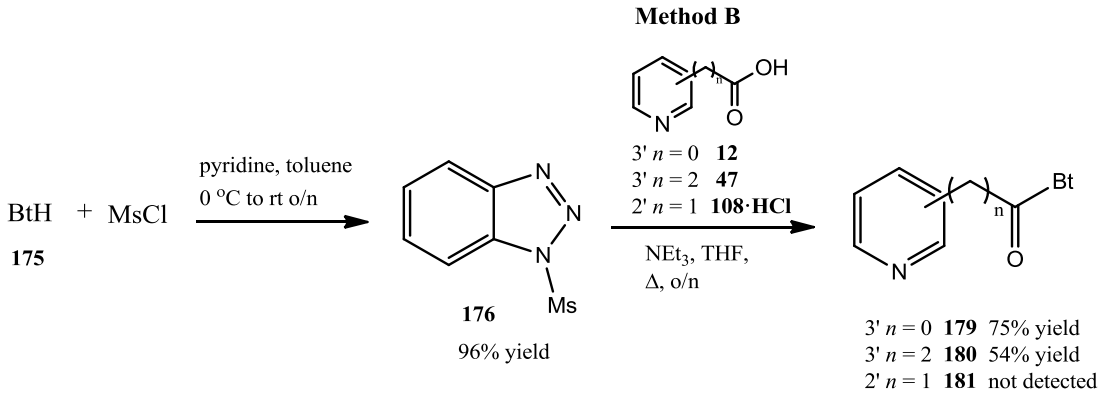


Figure 2.29: ^{1}H NMR (300 MHz, $CDCl_3$) spectrum and expansion of characteristic benzotriazole signals as well as ^{13}C NMR (75.5 Hz, $CDCl_3$) values of acylbenzotriazole 178

Having successfully synthesised acylbenzotriazole **178**, a series of pyridyl and pyridone acylbenzotriazoles **178-189** were identified as targets. While compound **179** has previously been reported by Katitzky,[56] none of the other acylbenzotriazoles **178** and **180-189** have been synthesised previously.

In the reactions to form unsubstituted pyridine derivatives **179-181**, Method B, which has been reported to be compatible with pyridines, was employed. Although preparation of nicotinic acid-derived acylbenzotriazole **179** has been reported by Katritzky,[56] the 3-(pyridin-3-yl)propanoic acid analogue **180** and pyridylacetic acid derivative **181** have not been synthesised previously.

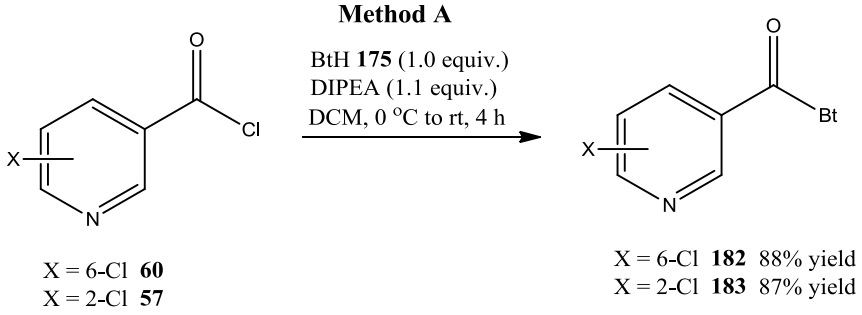
For Method B, acylation occurs *via* reaction of carboxylic acid with mesylated benzotriazole (BtMs) precursor **176** (**Scheme 2.76**). Following Katritzky's preparation of BtMs **176**,[56] mesyl chloride was reacted with 1*H*-benzotriazole **175** and pyridine at 0 °C in distilled toluene, followed by warming to room temperature overnight. While purification of the crude product was accomplished by recrystallisation from benzene in the literature,[56] the crude product **179** obtained in quantitative yield in this work was in general deemed sufficiently pure to use in the synthesis of the acylbenzotriazoles.



Scheme 2.76

Acylbenzotriazoles **179** and **180** derived from nicotinic acid **12** and 3-pyridylpropanoic acid **47** were successfully isolated in 75% and 54% yield respectively following reaction with BtMs **176** and triethylamine in THF (**Scheme 2.76**). Interestingly, when this method was applied to **108**·HCl, the acylbenzotriazole was not identified; however, as discussed earlier (**Section 2.3.1.3.3.1**), it is possible that the pyridylacetic acid was present as the hydrochloride salt, which is likely to have affected the acylbenzotriazole formation.

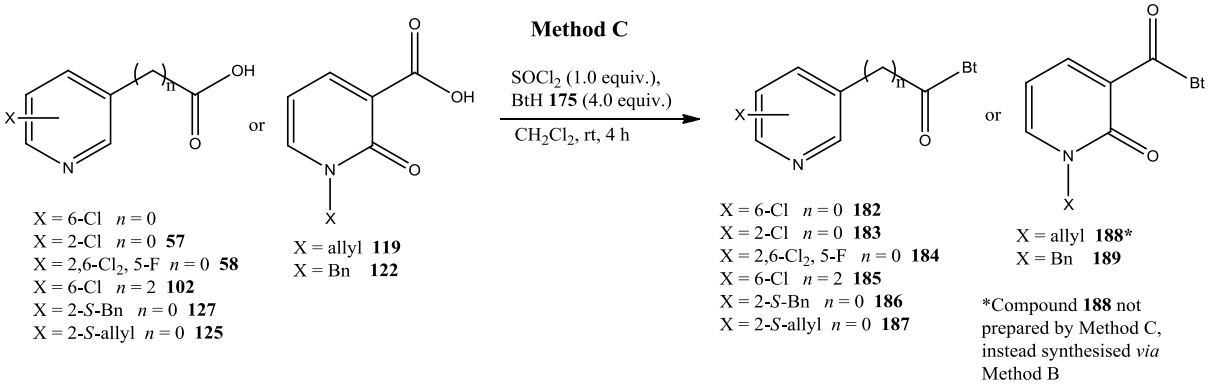
The traditional approach for acylbenzotriazole synthesis (Method A) using acid chlorides with 1*H*-benzotriazole in the presence of base was utilised in the preparation of halogenated derivatives **182** and **183**, which were obtained as white solids in excellent yield (**Scheme 2.77**).



Scheme 2.77

While Method A enabled formation of the acylbenzotriazoles in high yields, the choice of Methods B and C to prepare other pyridyl substrates was due to the possible lability of the acid chlorides from these compounds. Thus, in instances where the stability of the acid chloride is in question, Methods B and C avoiding the isolation of pyridyl acid chlorides were

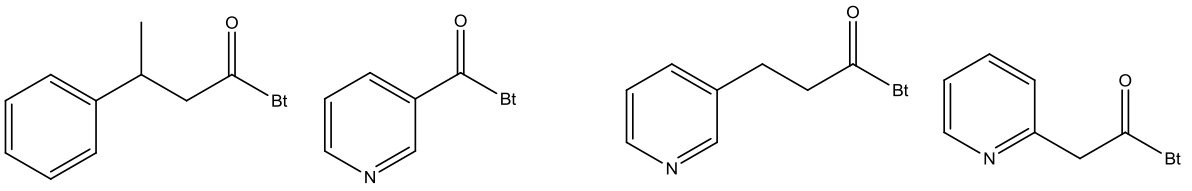
employed. To this end, Method C was employed in the synthesis of acylbenzotriazoles **182-187** and **189** (**Scheme 2.78**) in addition to either Method A and B for the particular compound (see **Figure 2.30**). Successful synthesis of substrates **182-187** and **189** was achieved in all cases using Method C, however, the isolated yields of the acylbenzotriazoles ranged from low to moderate (**Figure 2.30**). Notably, the results obtained refer to single experiments and the reaction conditions were not optimised during the course of this work.



Scheme 2.78

In the chromatographic purification of the acylbenzotriazoles, the samples often contained 1*H*-benzotriazole **175**, which co-eluted with the purified products. Elimination of this starting material in literature reports is usually achieved by washing with aqueous acid and an acidic workup was carried out when Method A was employed. However, in some cases using Methods B and C, the isolated yields were low and elimination of the side product **175** was not attempted due to possible loss of acylbenzotriazole attributed to protonation of the basic pyridine ring. As the presence of 1*H*-benzotriazole **175** did not have a deleterious effect on the subsequent reaction to form the 1,3-diketone, in general the acylbenzotriazoles could be progressed in the synthesis despite the presence of 1*H*-benzotriazole **175** as an impurity.

A summary of the acylbenzotriazoles prepared, **178-189**, as well as the respective isolated yields and melting points are shown below (**Figure 2.30**). It is worth noting that these melting points are for samples which contain 1*H*-benzotriazole **175**, while the yields given here are not corrected for this impurity.

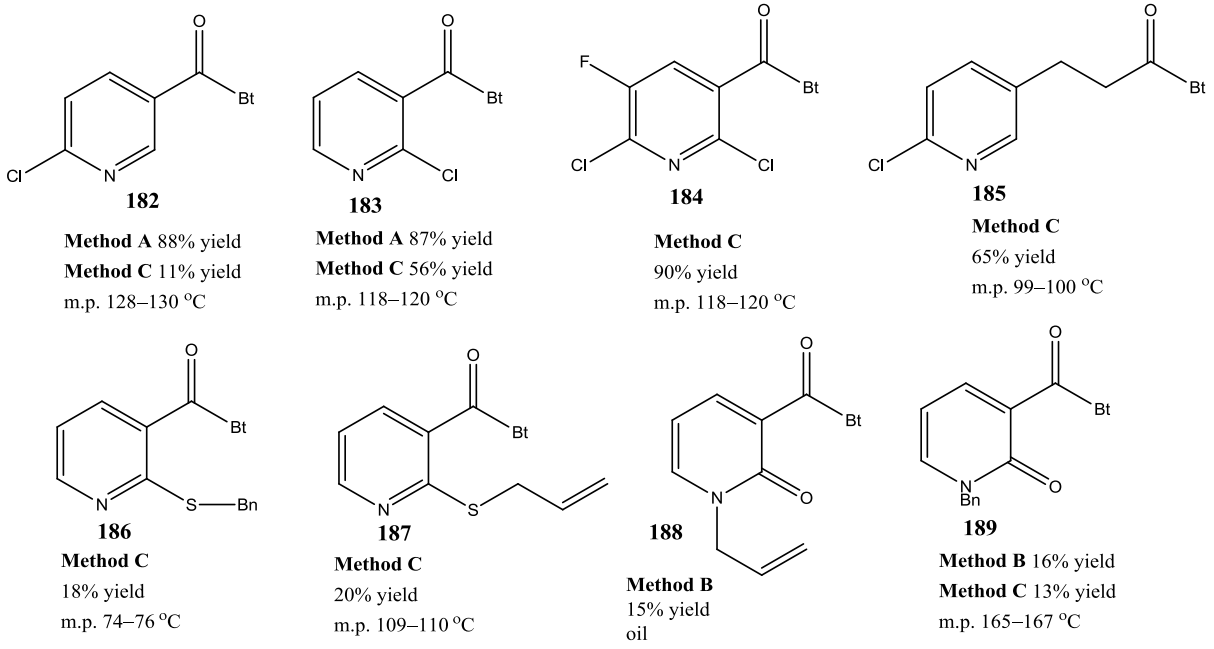


178
Method C
88% yield
m.p. 62–64 °C

179
Method B
75% yield
m.p. 87–89 °C
(Lit.,[35] 86–89 °C)

180
Method B
54% yield
m.p. 82–84 °C

181
Method B
not detected



Reaction conditions: **Method A:** Acid chloride, base.
Method B: $MeSO_2Bt$, Et_3N, THF at 60 °C.
Method C: $SOCl_2$, BtH (3 or 4 equiv.), CH_2Cl_2 (or THF), 23 °C.

Figure 2.30: Summary of acylbenzotriazoles synthesised using Methods A–C

In conclusion, ready access to a series of pyridyl and pyridone acylbenzotriazoles is possible and these are stable compounds which can be readily handled and stored. While any of the three methods leads to the acylbenzotriazoles, in general, where the acid chloride can be obtained as a precursor, Method A employing the acid chloride provides the highest yield. Interestingly, compounds **188** and **189** represent the first examples of successful synthesis of pyridone-containing acylbenzotriazoles.

Single crystal analysis was carried out on 6-chloro-3-substituted pyridylacylbenzotriazole **184** and the *N*-benzyl acylbenzotriazole **189**, adding further confirmation of synthesis of acylbenzotriazoles. The X-ray crystal structure of **184** (**Figure 2.31**) is clearly planar as indicated by the O4'-C1'-N1-N2 and C3"-C3'-C2'-C1' torsion angle of 179.72° and 176.58° respectively. In contrast, significant deviation from planarity is observed for the X-ray crystal structure of the *N*-benzyl acylbenzotriazole **189** (**Figure 2.32**). Notable deviations include the dihedral angles between O2'-C1'-C3"-C4" (57.96°), between C2"-N1"-C8-C9 (72.20°) and between C3"-C1'-N1-C7A (–170.80°).

Examination of the X-ray crystal structure of **184** reveals two distinct and weak intermolecular C–H···N interactions of 2.52 and 2.50 Å (**Figure 2.31**). The unit cell is composed of repeating C(11) and C(6) chains along the *c* and *a* axes respectively. In addition, two weak C–H···N interactions (2.57 Å) were also observed in the crystal structure of *N*-benzyl acylbenzotriazole **189** (**Figure 2.32**).

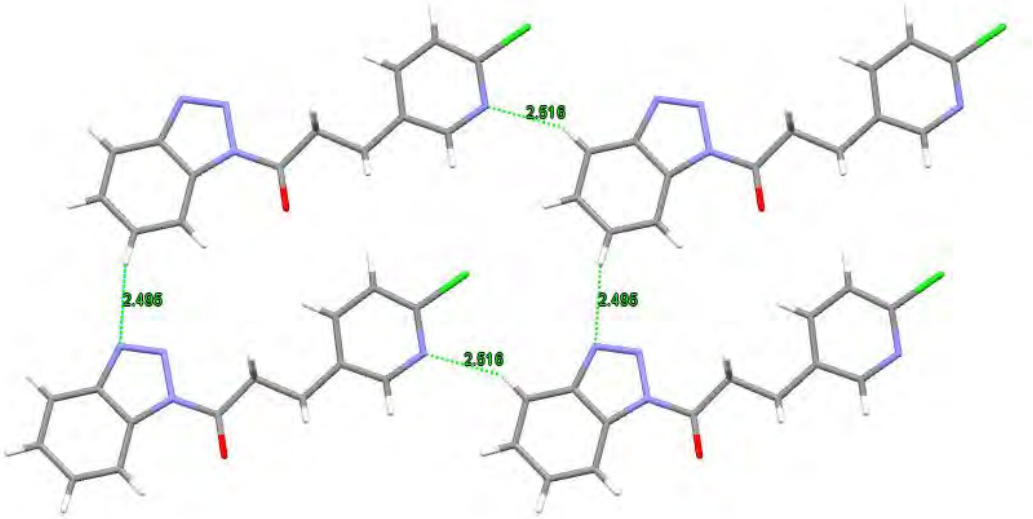


Figure 2.31: X-ray crystal structure of 184

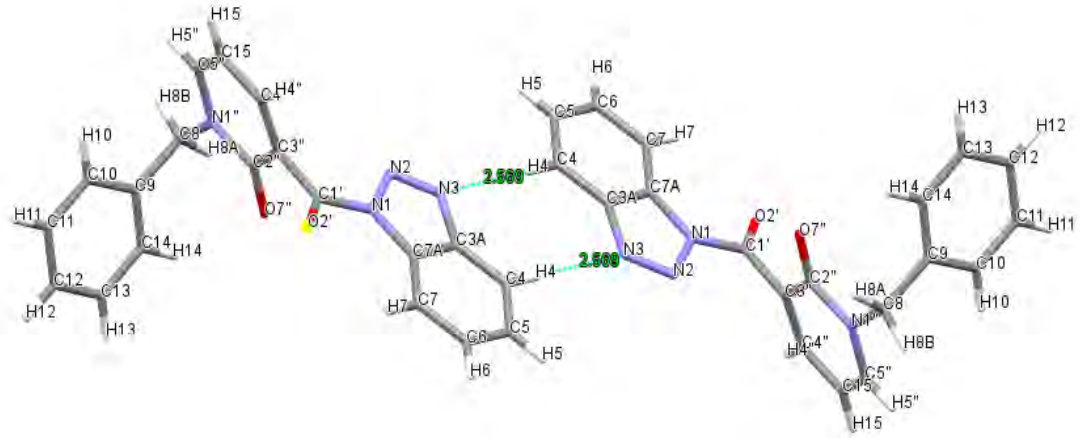
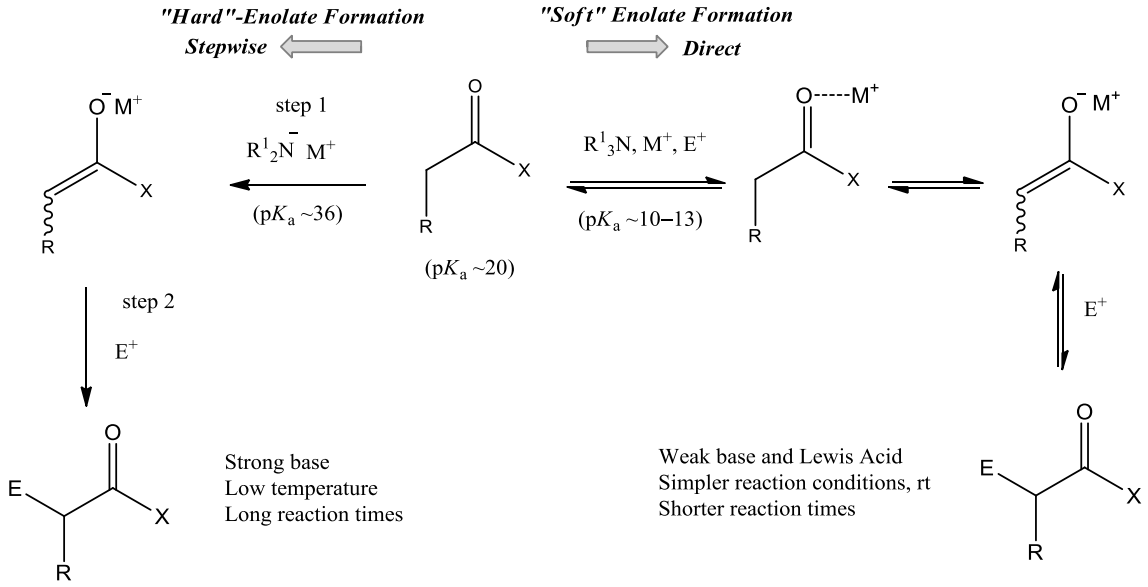


Figure 2.32: X-ray crystal structure of 189

2.3.2.3 Synthesis of 1,3-diketones

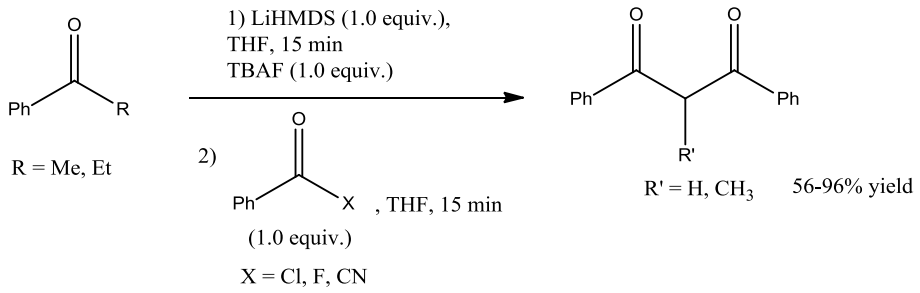
Following efficient synthesis of a range of pyridine and pyridone substituted acylbenzotriazoles **178-180**, **182-189**, the penultimate step in the α-diazoketone synthesis involved formation of α-substituted diketones, which were subsequently used as substrates for the diazo transfer protocol (**Section 2.3.2.4**). Generally, this carbon–carbon bond forming methodology involves reaction of a ketone with a strong base (*e.g.* LDA, LiHMDS) to form the enolate, which then reacts with either the acid chloride or acylbenzotriazole. However, in more recent times it has been demonstrated that the ketone enolate can be prepared *via* soft or hard enolisation of the ketone, followed by addition of the acylating agent to generate the acylated product.

Hard enolisation comprises deprotonation of the ketone using a strong non-nucleophilic base (*e.g.* LDA, pK_a ~36) and is followed by a stepwise addition of the electrophile and the reactions are carried out under anhydrous conditions at low temperatures.[198,199] The soft enolisation approach uses a weak base such as *N*,*N*-diisopropylethylamine (Hünigs base, pK_a ~10–13) allied with a Lewis Acid (*e.g.* $MgBr_2 \cdot OEt_2$) and these reactions can be conducted under milder conditions.[200] The soft enolisation proceeds in a direct manner and is reversible unlike the irreversible and stepwise hard enolisation. Both enolisation methods are illustrated below (**Scheme 2.79**).

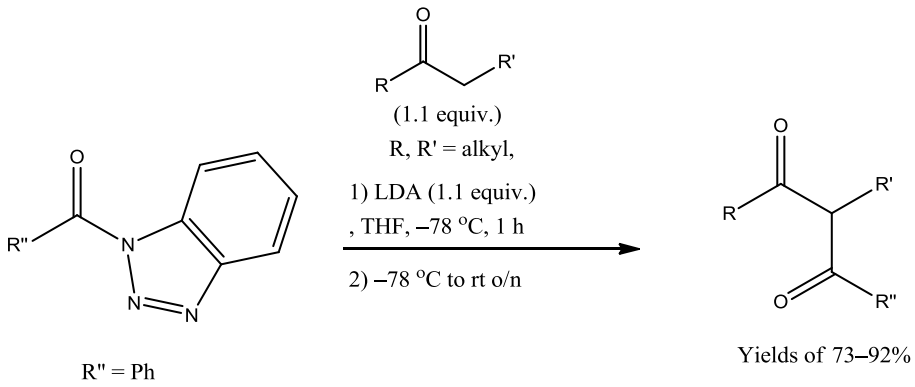


Scheme 2.79: Hard and soft enolisation (diagram adapted from Coltart *et al.*)[200]

Substituted 1,3-diketones have been prepared using both hard and soft enolisation procedures with regioselective formation of products. Wiles *et al*. have reported efficient synthesis of 1,3-diketones *via* lithium enolates using acid halides and cyanides for three ketone substrates (acetophenone, propiophenone and cyclohexanone) (**Scheme 2.80**).[198] Katritzky has also disclosed regioselective preparation of β-diketones from ketone enolates (**Scheme 2.81**) using *N*-acylbenzotriazoles as substrates for this methodology.[199] Katritzky has claimed the advantage of using *N*-acylbenzotriazoles for the enolate condensation rests on their neutral character and ease of accessibility.

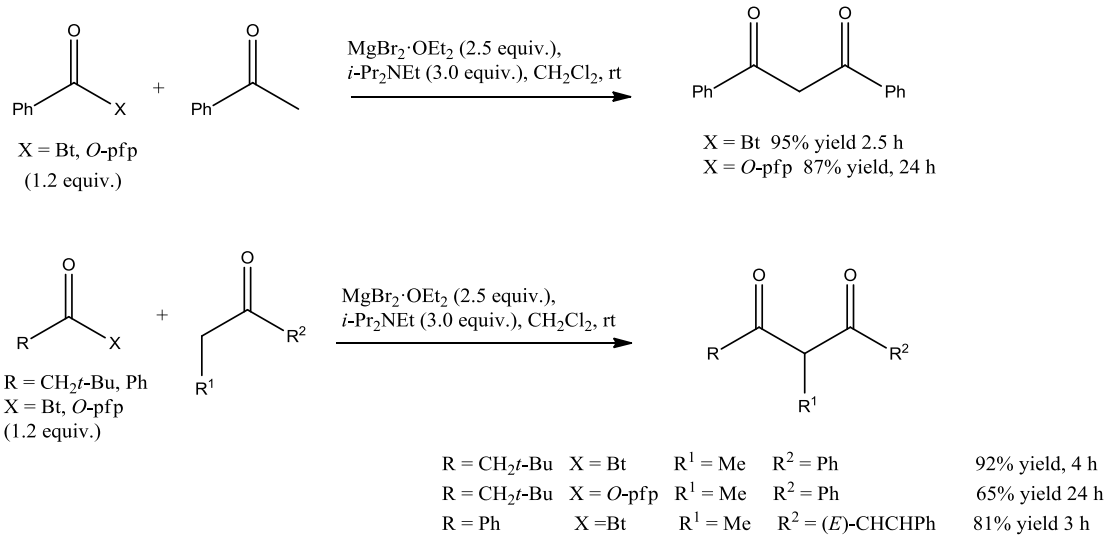


Scheme 2.80



Scheme 2.81

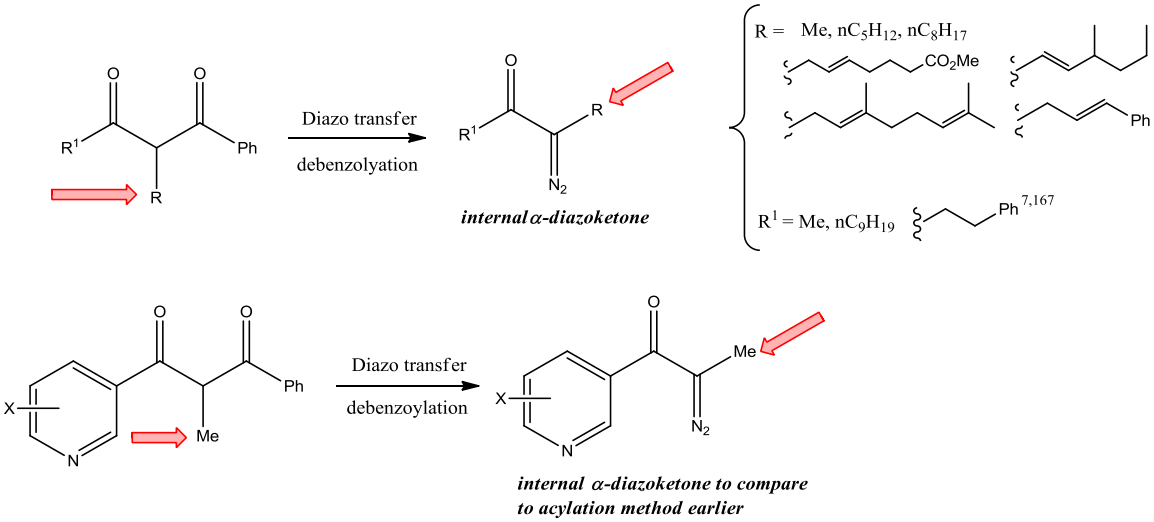
Coltart has carried out synthesis of 1,3-diketones, this time employing the soft enolisation method using magnesium bromide diethyl etherate as Lewis acid and *N*,*N*-diisopropylethylamine as base with a range of ketones (**Scheme 2.82**).[200] In the synthesis of 1,3-diketones, this approach proved particularly successful for *N*-acylbenzotriazoles and *O*-pentafluorophenol (*O*-pfp) esters. The authors have reported reaction conditions involving "*untreated*" dichloromethane as solvent at room temperature with the reaction times 2–4 h for the acylbenzotriazoles and ~24 h for the *O*-pfp esters. This soft enolisation methodology has also previously been employed by Coltart in the preparation of thioesters *via* an aldol reaction.[201,202]



Scheme 2.82: Synthesis of 1,3-diketones using Bt- and *O*-pfp-mediated acylation

Through the initial formation of α-alkylated 1,3-diketones containing a variety of alkyl groups by these acylation methods, this potentially allows the construction of internal α-diazoketones *via* selective debenzoylation, following diazo transfer to the α-substituted diketone (**Scheme 2.83**). In our work, the key aspect is the generation of the substituted 1,3-diketone possessing an α-methyl group. The strategic placement of the methyl group results in the assembly of internal α-diazoketones following selective debenzoylation, which enables

a direct comparison to those prepared earlier in this work using the acylation approach (**Section 2.3.1.5.1**). Previously, work by Taber[168,203] as well as Ford[167] and McDowell[7] in our lab have successfully synthesised internal α-diazoketones using this methodology.



Scheme 2.83: Importance of substrate control in the synthesis of 1,3-diketones and α-diazoketones

Three methods were employed to prepare the β-diketones in this work;

a) Method A: Hard enolisation using lithium bis(trimethylsilyl)amide (LiHMDS),

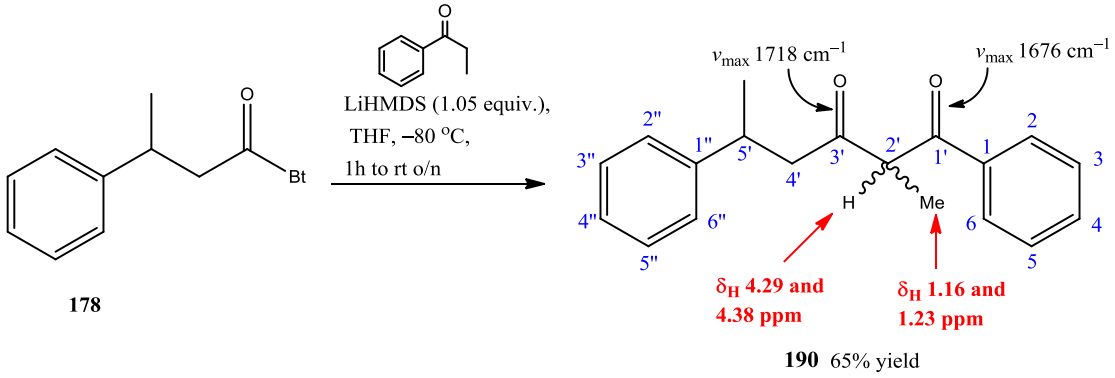
b) Method B: Soft enolisation using $MgBr_2.OEt_2$ and *N*,*N*-diisopropylethylamine, and

c) Method C: Hard enolisation using LDA.

Preliminary investigation involved the phenyl substituted acylbenzotriazole **178**, which was brought forward for 1,3-diketone formation using a modified version of the procedure outlined by Katritzky (Method A) (**Scheme 2.84**).[199] LiHMDS was added to a THF solution of propiophenone at −80 °C and a THF solution of the acylbenzotriazole **178** was added to the resulting enolate at the same temperature. The reaction mixture was warmed to room temperature overnight and the crude β-diketone isolated as a yellow oil after an acidic workup using aqueous hydrochloric acid. Two aqueous hydrochloric acid washes were carried out on the mixture to remove excess 1*H*-benzotriazole **175**, which can co-elute with purified 1,3-diketones. For the pyridine substrates, this was later replaced by use of aqueous saturated ammonium chloride to quench the reaction due to susceptibility of protonation of the pyridine ring by acid, leading to possible loss of product.

The purified β-diketone **190** was isolated after column chromatography in 65% yield with the ^{1}H NMR spectroscopic analysis clearly showing the formation of the β-diketone. There was also clear evidence for the formation of two diastereomers in the ^{1}H NMR spectrum, observed in a diastereomeric ratio of ~50 : 50 (**Figure 2.33**). The characteristic signals in the ^{1}H NMR

spectrum are the diastereomeric α-methine signals, C(2')<u>H</u>CH$_3$, observed as a pair of quartets at δ_H 4.29 and 4.38 ppm and the neighbouring diastereomeric α-methyl signals, C(2')C<u>H</u>$_3$, identified as two doublets at δ_H 1.16 and 1.23 ppm (2 × *J* 6.8 Hz). Two carbonyl stretches were also observed in the infrared spectrum at ν_{max} 1718 and 1676 cm^{-1}, providing additional structural identity for the 1,3-diketone. Many β-diketones exist as an equilibrating mixture of keto and enol forms; however, in this case, β-diketone **190** appeared to be isolated as the keto form with no indication of the enol tautomer. ^{1}H NMR and infrared Spectroscopic characteristics obtained for 1,3-diketone **190** were in agreement with those previously described by Ford in our laboratory.[167]



Scheme 2.84

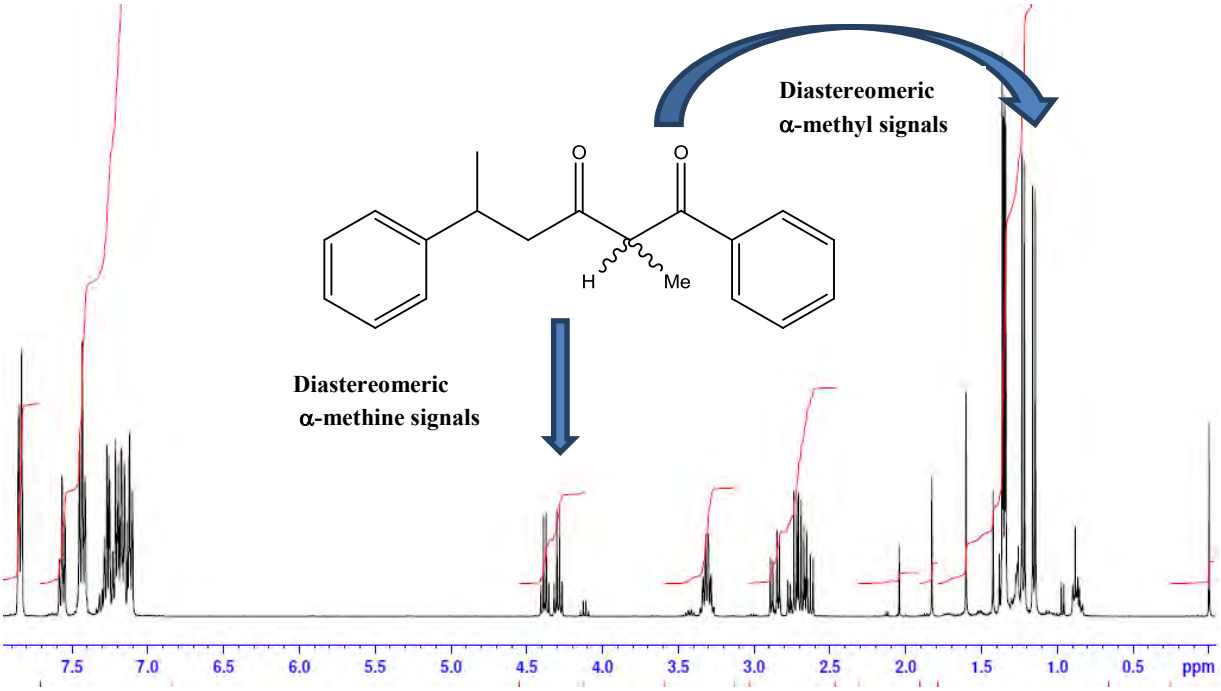
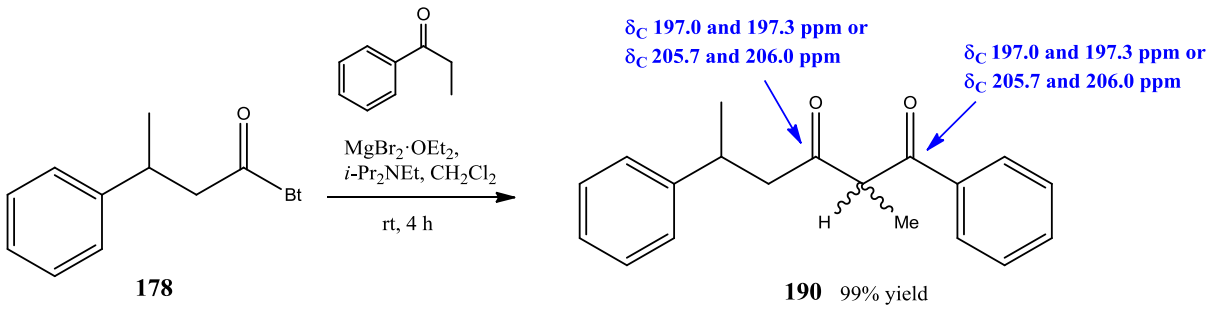


Figure 2.33: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of β-diketone 190

Following formation of β-diketone **190** using the hard enolisation approach, preparation of the same β-diketone **190** using the soft enolisation strategy developed by Coltart[200] (Method B) was next explored (**Scheme 2.85**).



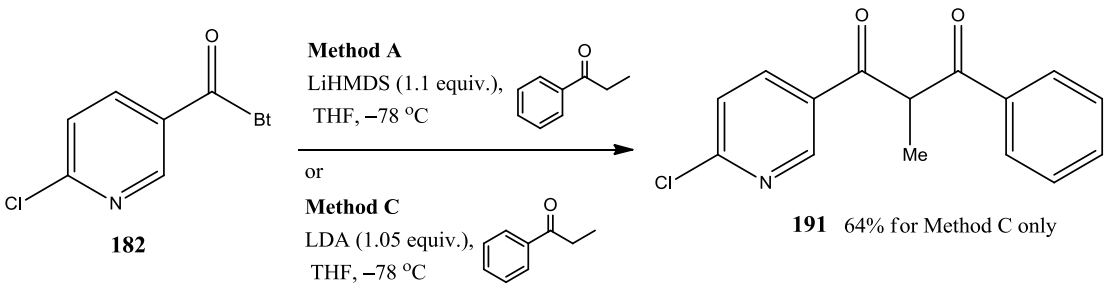
Scheme 2.85: ^{13}C NMR signals (75.5 MHz, $CDCl_3$) for 190

In contrast to Method A, the reaction does not require the multi-step formation of the deprotonated intermediate and the acylated product. Reaction conditions for Method B consisted of dropwise addition of propiophenone to a stirring solution of $MgBr_2 \cdot OEt_2$ and **178** in doubly distilled dichloromethane followed by addition of *N*,*N*-diisopropylethylamine to the reaction mixture and the reaction was found to be complete after 4 h. The β-diketone **190** was isolated in 99% yield following chromatography, providing spectroscopic characteristics identical to those obtained using Method A. In the ^{13}C NMR spectrum of **190**, two diastereomers were identified as two sets of signals observed for all the carbons in the spectrum. The distinctive signals for the carbonyl groups were located at δ_C 197.0 and 197.3 ppm for one set of signals and δ_C 205.7 and 206.0 ppm for the corresponding set of signals. While it is likely the values at δ_C ~197 ppm are ascribed to C(1')=O adjacent to the phenyl ring and signals at δ_C ~206 ppm are attributed to C(3')=O adjacent to the linker chain, a definitive assignment is not possible here. In addition, definitive assignment of the two carbonyls is not provided for related phenyl substituted 1,3-diketones reported in the literature. Thus, 2D NMR correlation experiments would be required to verify an assignment of the carbonyl signals. Minor additional peaks were also detected in the ^{13}C NMR spectrum, which could be ascribed to the enol tautomer as they do not appear to belong to the diastereomeric mixture.

Following successful formation of β-diketone **190** by both enolisation methods for the phenyl substituted acylbenzotriazole **178**, the next step involved applying these methods to the pyridine-containing acylbenzotriazoles. Initial efforts employed Methods A and C using LiHMDS and lithium diisopropylamine (LDA) as base in the hard enolisation, while later attempts involved the soft enolisation method.

The first substrate investigated for the stronger base-mediated strategy was 6-chloropyridine benzotriazole **182** (**Scheme 2.86**). Using Method A, as employed for the phenyl acylbenzotriazole **178**, the reaction did not proceed with complete absence of characteristic β-diketone signals in the crude ^{1}H NMR spectrum. It was possible that there was some degradation of the commercial LiHMDS solution which would hinder initial formation of the lithium enolate. Also, because of difficulty in titrating this solution, it was difficult to determine the accurate molarity of the solution that was used in the reaction.

Subsequently, Method C utilising LDA as the base was investigated. The freshly generated LDA solution was found to be very effective in this reaction and the purified novel 1,3-diketone **191** was isolated in 64% yield after chromatography.

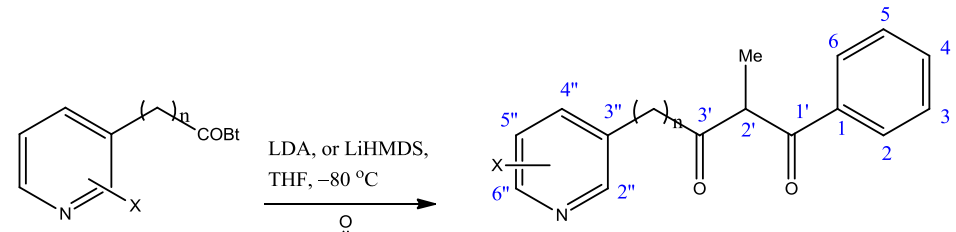


Scheme 2.86

After successful synthesis of the pyridine-containing 1,3-diketone **191** employing Method C using LDA as the base, this procedure was used in subsequent reactions for pyridine substituted acylbenzotriazoles **183** and **185**. Employing this procedure, β-diketone **196** was prepared but in low yield and less efficiently than seen for **191**. Attempted preparation of diketone **192** *via* method C only yielded a trace of diketone, instead mainly generating byproduct **201** as the main component in 20% yield (**Table 2.12**, entry 2).

It appeared that the use of fresh sample of strong base had a dramatic influence on the efficiency of the reaction. In light of this, a fresh sample of commercially available LiHMDS solution was used in subsequent reactions with Method A used in the preparation of the pyridine **191-198** (**Scheme 2.87**) and pyridone **199-200** β-diketones (**Scheme 2.88**). An important point is that the subsequent reactions using Method A were undertaken over the course of a few days to ensure that the commercial base did not decompose over time and impinge on the efficiency of the reaction.

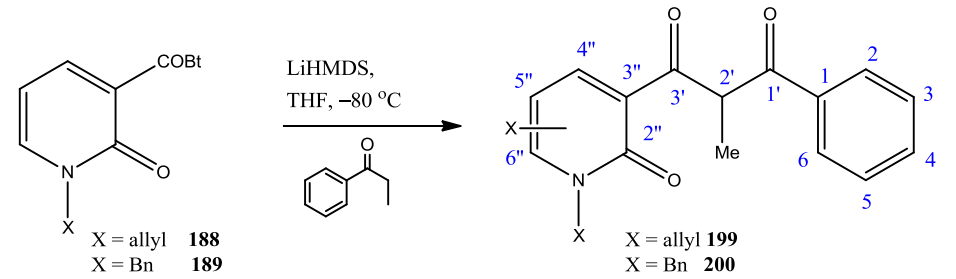
While efficient formation of 1,3-diketones was achieved in most cases, attempted formation of 1,3-diketone from the unsubstituted acylbenzotriazole **179** indicated no evidence of β-diketone **193** (**Table 2.12**, entry 3). However, acylation of the longer-chain analogue **180** did result in formation of 1,3-diketone **194** in low yield (**Table 2.12**, entry 4). Similar to Method C (**Scheme 2.86**), attempted formation of **192** using Method A resulted in generation of byproduct **201** as the major component, while in this case, isolable 1,3-diketone **192** was also recovered in 14% yield (**Table 2.12**, entry 2, Method A). The analogous byproduct **202** was also identified in the crude ^{1}H NMR of 1,3-diketone **195**, however, this compound was not isolated. A summary of the 1,3-diketones **191-200** prepared, as well as predominant byproducts in some instances is summarised below (**Table 2.12**).



X = 6-Cl $n = 0$ **182**
X = 2-Cl $n = 0$ **183**
X = H $n = 0$ **179**
X = H $n = 2$ **180**
X = 2,6-Cl_2, 5-F $n = 0$ **184**
X = 6-Cl $n = 2$ **185**
X = 2-*S*-Bn $n = 0$ **186**
X = 2-*S*-allyl $n = 0$ **187**

X = 6-Cl $n = 0$ **191**
X = 2-Cl $n = 0$ **192**
X = H $n = 0$ **193**
X = H $n = 2$ **194**
X = 2,6-Cl_2, 5-F $n = 0$ **195**
X = 6-Cl $n = 2$ **196**
X = 2-*S*-Bn $n = 0$ **197**
X = 2-*S*-allyl $n = 0$ **198**

Scheme 2.87: General numbering scheme for pyridine-containing β-diketones



X = allyl **188**
X = Bn **189**

X = allyl **199**
X = Bn **200**

Scheme 2.88: General numbering scheme for 2-pyridone-containing β-diketones

Table 2.12 *Isolated yields of 1,3-diketones* ***191-200*** *using Methods A and C*

Entry	Bt (X =)	*n* =	Diketone	Yield (%)[a]	
				Method A	Method C
1	6-Cl **182**	0	**191**	38	64
2	2-Cl **183**	0	**192**	14+41 of **201***	0+20 of **201***
3	H **179**	0	**193**	0	–
4	H **180**	2	**194**	10	–
5	2,6-Cl_2,5-F **184**	0	**195**	31**	–
6	6-Cl **185**	2	**196**	67	23
7	2-*S*-Bn **186**	0	**197**	57	–
8	2-*S*-allyl **187**	0	**198**	68	–
9	allyl **188**	0	**199**	32	–
10	Bn **189**	0	**200**	67***	–

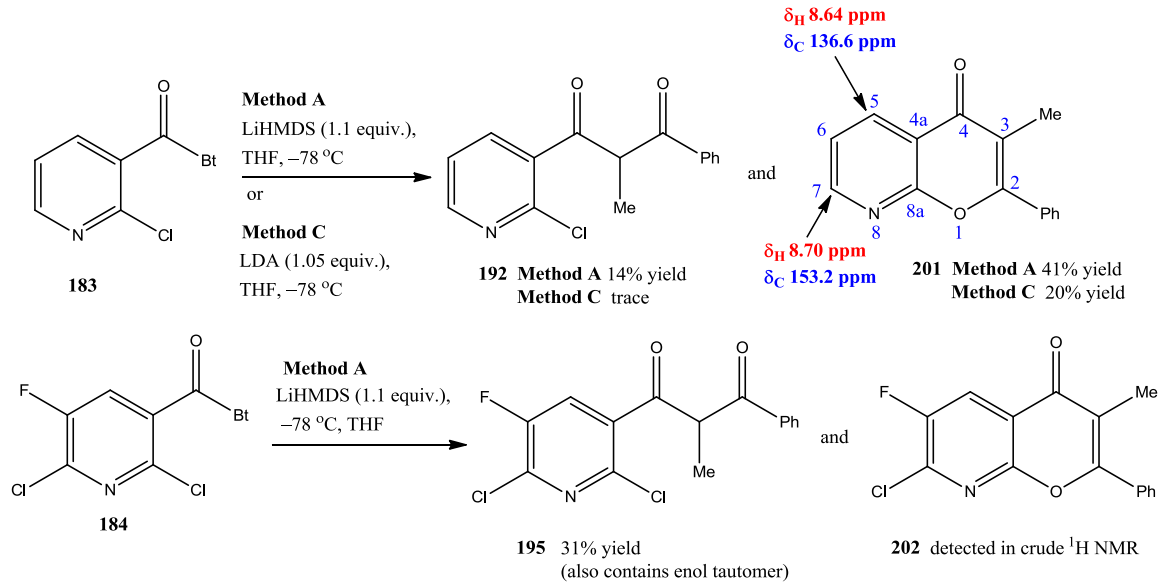
[a] Isolated yield of products after column chromatography.
* Major product isolated corresponded to byproduct **201.**
** Crude product contains ~13 mol% of side product **202** tentatively assigned by peaks at δ_H 2.20 ppm and one of δ_H 8.05 or 8.18 ppm. Purified product contains a mixture of 1,3-diketone **195** and enol tautomer (~32 mol%) and enol is assigned by signals at δ_H 1.84 ppm, 7.58 ppm, 7.59-7.64 ppm and 16.34 ppm.
*** 1,3-diketone **200** co-eluted with 1*H*-benzotriazole **175** so the yield is an overestimate.

Each of these 1,3-diketones **191**, **192** and **194-200** is a novel compound and they were fully characterised during the course of this work. These compounds were isolated as oils and appear to exist exclusively as the diketones with minor exception that the enol tautomer is present (~32 mol%) along with 1,3-diketone **195** (**Table 2.12**, entry 5). Characteristic signals in the ^{1}H NMR spectrum include a doublet at δ_H ~1.40–1.81 ppm for the α-methyl group and as a quartet at δ_H ~4.46–6.00 ppm ascribed to the α-methine proton

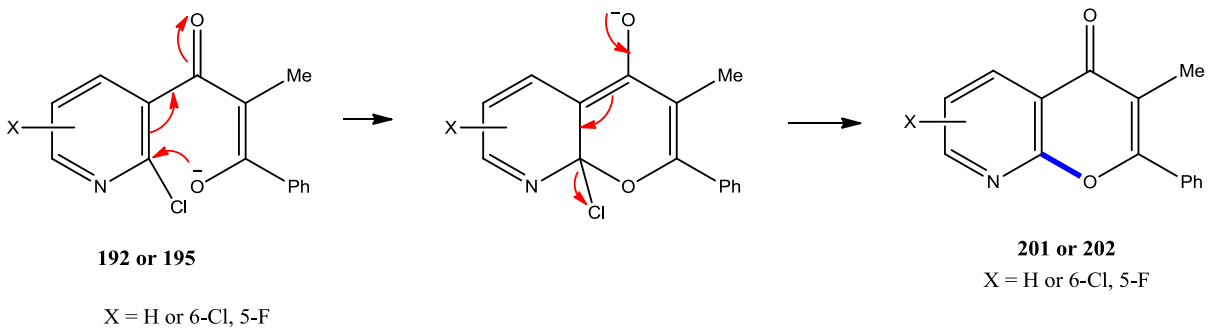
In the case of the *N*-benzyl diketone **200**, this purified product was found to co-elute with the side product, 1*H*-benzotriazole **175**, even after repeated chromatography and varying the eluent system from ethyl acetate/hexane to methanol/dichloromethane. By comparing a standard sample of isolated 1*H*-benzotriazole **175** (from other attempts involving formation of β-diketones) with the impure mixture here, it was possible to distinguish the signals for the β-diketone **200** from the inseparable 1*H*-benzotriazole **175** in both the ^{1}H NMR and ^{13}C NMR spectra. The signals for **175** in the ^{1}H NMR spectrum were observed as distinctive multiplets at δ_H 7.43 and δ_H 7.94 ppm, while the corresponding signals were detected at δ_C 115.1, 126.1 and 139.0 ppm in the ^{13}C NMR spectrum.

Very interestingly, on carrying out attempted acylation of 2-chloro substituted acylbenzotriazole **182** *via* Method C using propiophenone and LDA (**Table 2.12**, entry 2, Method C), the chromone analogue **201** was isolated as a white solid in 20% yield as the major component with a trace amount of an impure sample of 1,3-diketone **192** detected (**Scheme 2.89**). Structural identity of **201** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, as well as nominal and high resolution mass spectrometry, the latter clearly showing the loss of the chlorine isotope pattern. Employment of Method A with the same substrate (**Table 2.12**, entry 2, Method A) indicated formation of the chromone analogue **201** as well as formation of the 1,3-diketone **192** in the crude ^{1}H NMR spectrum (76 : 24 of **192** : **201**). However, following chromatography, 1,3-diketone **192** was isolated in 14% yield, while chromone analogue **201** was isolated as the major component from the reaction mixture in 41% yield. The corresponding chromone analogue **202** was also identified as a minor component in the crude ^{1}H NMR spectrum from attempted acylation of acylbenzotriazole **184** using Method A (**Table 2.12**, entry 5) as well as 1,3-diketone **195** as the major component of the mixture (87 : 13 of **195** : **202**). Following chromatography, the impure 1,3-diketone **195** was isolated in 31% yield containing additional signals in the ^{1}H NMR spectrum, assumed to belong to the enol tautomer (~32 mol%).

The formation of chromone analogue 3-methyl-2-phenyl-4*H*-pyrano[2,3-b]pyridin-4-one **201** is thought to arise from nucleophilic aromatic substitution of the enolate of the diketone into the C(2")-Cl bond of the pyridine ring, as illustrated in **Scheme 2.90** below.



Scheme 2.89: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125.8, $CDCl_3$) values of 201 and identification of side product 202



Scheme 2.90: Proposed mechanism for formation of chromone analogues 201 and 202

Since protons in the α-position [C(2)H or C(6)H] to the ring nitrogen are more deshielded and have smaller coupling constants than protons in the γ-position [C(4)H],[103] this allowed identification of signals for C(5)H and C(7)H in the ^{1}H NMR spectrum of **201** (**Scheme 2.89**). ^{1}H NMR spectroscopic analysis of **201** showed doublets of doublets at δ_H 8.64 ppm (*J* 7.6 and 2.0 Hz) and at δ_H 8.70 ppm (*J* 4.8 and 2.0 Hz). This indicated that the signal at δ_H 8.64 ppm corresponded to C(5)H, while the value at δ_H 8.70 ppm was ascribed to C(7)H. A ^{1}H–^{13}C HSQC experiment confirmed the assignment that the signal at δ_C 136.6 ppm corresponded to C(5)H and the value at δ_C 153.2 ppm was associated with C(7)H, while additional structural correlations of **201** were established by a ^{1}H–^{1}H COSY experiment. The formation of byproduct **201** can be attributed to the labile nature of the chlorine at the 2-position on the pyridine ring, which can be easily displaced.

An X-ray crystal structure of **201** was also obtained providing further structural confirmation and this is shown below (**Figure 2.34**). Solid state interactions of the crystal structure highlight a weak C–H···N interaction with a distance of 2.69 Å observed.

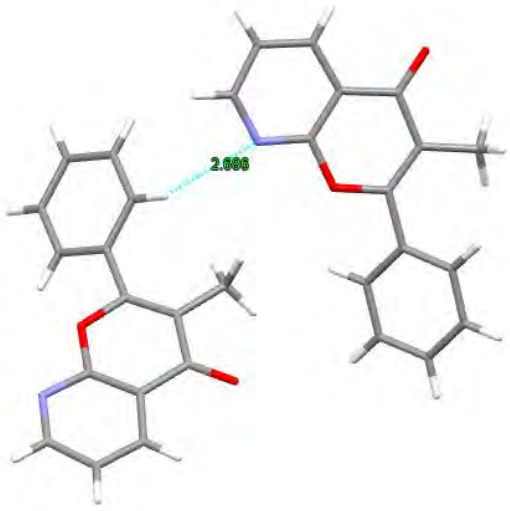
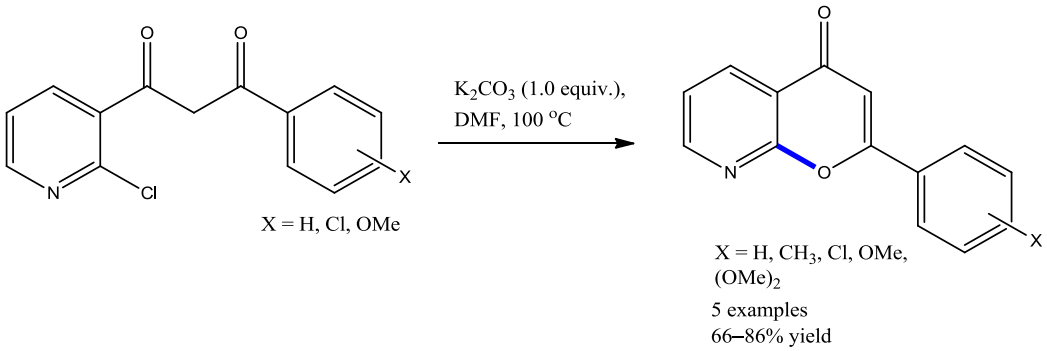


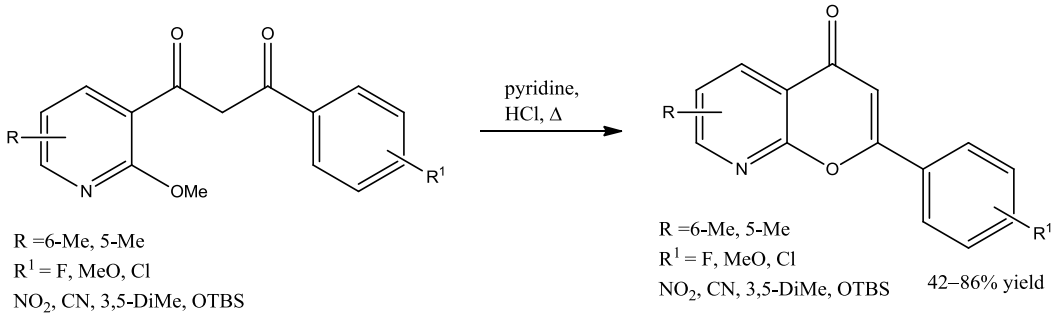
Figure 2.34: X-Ray crystal structure of 201

Similar substrates have been prepared by Fu and co-workers utilising a transition metal-free intramolecular Ullman-type *O*-arylation strategy for the base-promoted synthesis of chromone derivatives (**Scheme 2.91**).[204]



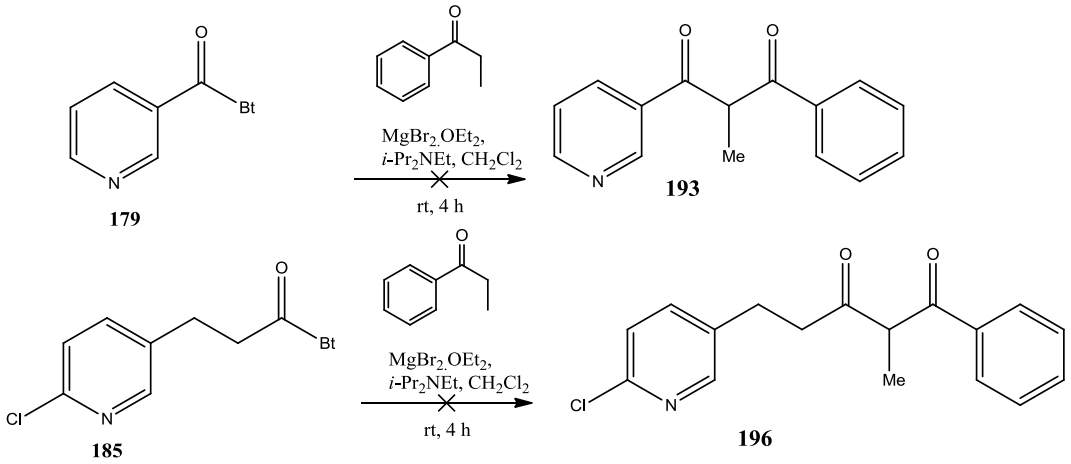
Scheme 2.91: Similar substrates prepared by Fu[204]

The 2-aryl-4*H*-pyrano[2,3]pyridine-4-one architecture is quite similar to flavonoid analogues synthesised by Hansen and co-workers (**Scheme 2.92**).[205] This flavone-type structural motif can be viewed as an important component in medicinal chemistry since the parent flavonoids possess numerous biological and pharmacological properties, including anticancer, antioxidative and anti-inflammatory activity.[206]



Scheme 2.92

With some success using the hard enolisation conditions, the soft enolisation approach (Method B) was next applied to the pyridine acylbenzotriazoles (**Scheme 2.93**). This method was investigated for acylbenzotriazoles, **179** and **185**, with the unsubstituted derivative **179** of particular interest since the formation of the desired β-diketone **193** had proven elusive using Method C. However, in both cases, there was an absence of the characteristic signals for the 1,3-diketones in the crude ^{1}H NMR spectrum. After purification by column chromatography, only the acylbenzotriazole starting materials were recovered.



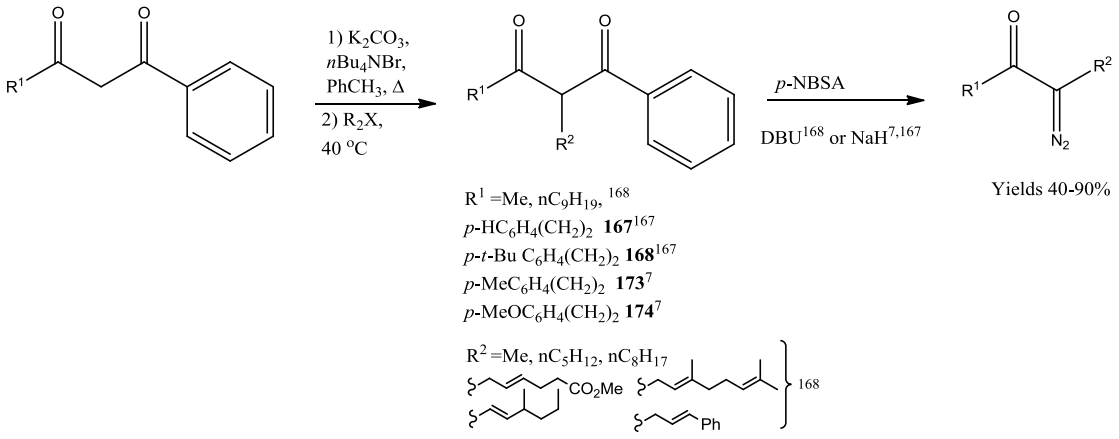
Scheme 2.93

This is surprising considering that acylbenzotriazole **178** in this work, as well as other aromatic acylbenzotriazoles prepared by Coltart allowed ready access to the corresponding 1,3-diketones *via* Method B.[200] It is worth noting that no heterocyclic acylbenzotriazoles were investigated by Coltart and co-workers in their work, suggesting that pyridine-containing acylbenzotriazoles may not be compatible with this soft enolisation methodology.

The 1,3-diketones **191**, **192** and **194-200** successfully synthesised were brought forward to diazo transfer reaction for the crucial step in preparing the internal α-diazoketones.

2.3.2.4 Formation of unsymmetrical α-diazoketones using diazo transfer methodology

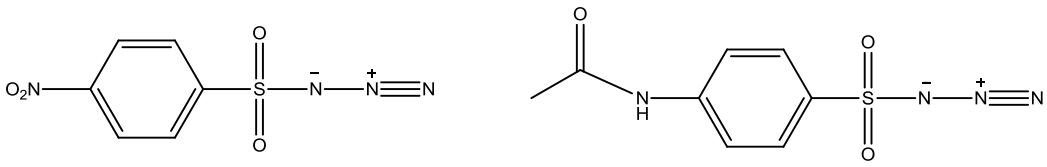
The diazo transfer method has been widely utilised in organic synthesis for the generation of α-diazocarbonyl compounds (see **Sections 1.2.2** and **3.3.1.2**). In 1995, Taber and co-workers reported the regioselective assembly of internal α-diazoketones and α-diazoesters *via* diazo transfer to unsymmetrical α-substituted 1,3-diketones using the combination of *p*-NBSA **166** as diazo transfer reagent and DBU as base (**Scheme 2.94**).[168] The interesting aspect of this particular diazo transfer process is concomitant debenzoylation with diazo transfer to furnish the internal α-diazocarbonyl compounds in one-pot from the unsymmetrical 1,3-diketones, with the reactions proceeding in good to excellent yields. In addition, Ford[167] and McDowell[7] in our research group have synthesised internal phenyl substituted α-diazoketones **167**, **168** and **173**, **174** (**Scheme 2.94**) employing Taber's debenzoylation diazo transfer methodology.



Scheme 2.94

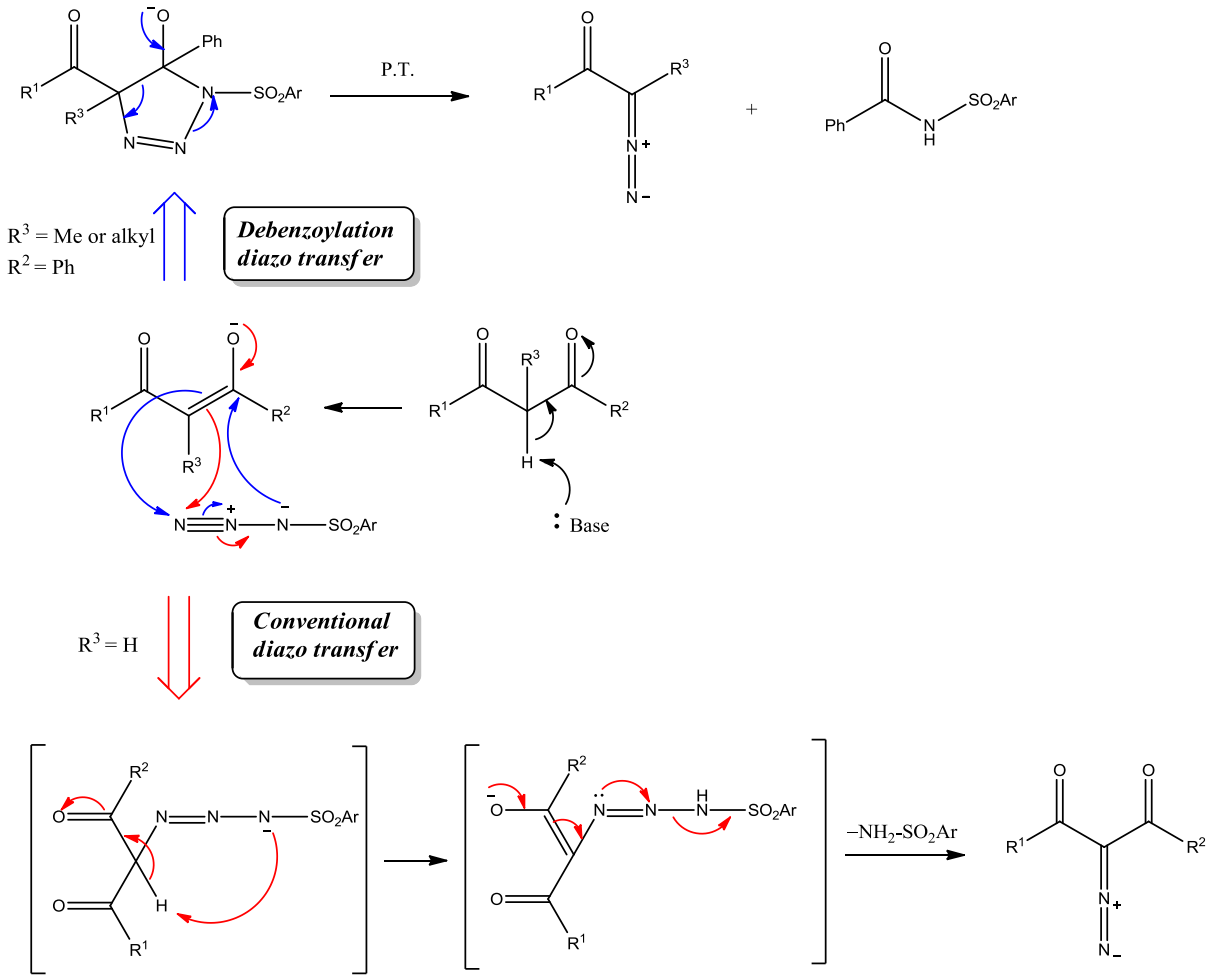
The diazo transfer reagent used in these reactions is *p*-nitrobenzenesulfonyl azide (*p*-NBSA) **166**. While other diazo transfer reagents such as *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) **203** have been used elsewhere in this work (**Chapter 3**, **Sections 3.3.1.2** and **3.3.3.2**), *p*-NBSA **166** was found from work by Taber[168] and Ford[167] in the Maguire group to be the best reagent for the construction of unsymmetrical α-diazoketones using diazo transfer with associated debenzoylation.

The structures of both diazo transfer reagents used in this project are illustrated below (**Figure 2.35**). The general reaction mechanism of conventional diazo transfer process, as well as the debenzoylation diazo transfer reaction is shown below (**Scheme 2.95**). In the debenzoylation procedure, the α-substituent on the 1,3-diketone prevents diazo transfer proceeding by the conventional route, which instead triggers debenzoylation to afford the α-diazocarbonyl product.



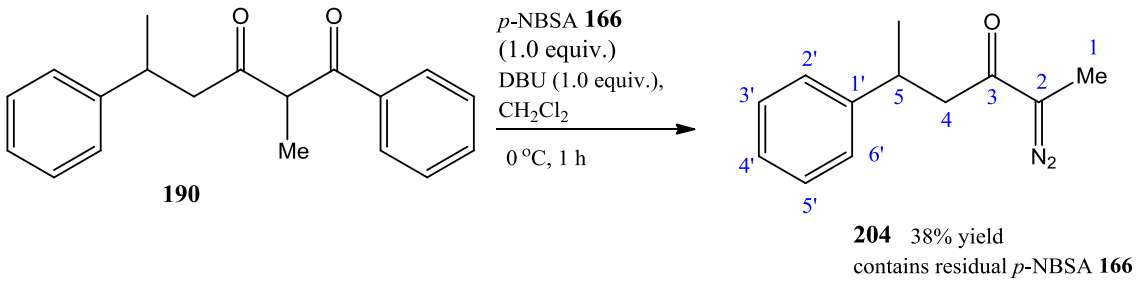
***p*-Nitrobenzenesulfonyl azide (*p*-NBSA) 166** **_____** ***p*-Acetamidobenzenesulfonyl azide (*p*-ABSA) 203**

Figure 2.35: Diazo transfer reagents used in this research



Scheme 2.95: Illustration of conventional diazo transfer and debenzoylation diazo transfer (proposed mechanism adapted from deformylative diazo transfer[207]) methods

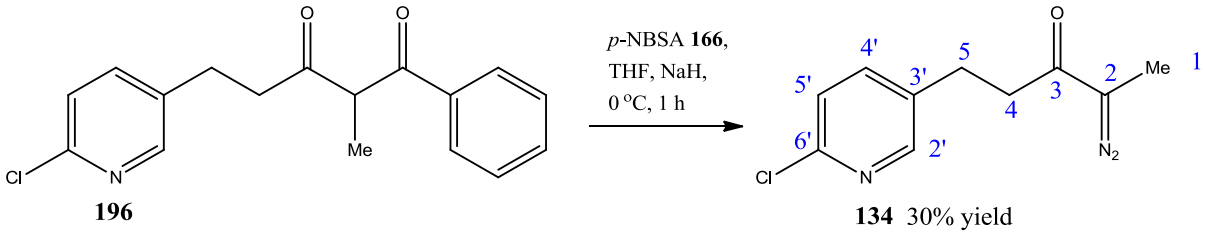
The 1,3-diketones **190**, **191** and **197-200** were used as substrates for diazo transfer to provide the unsymmetrical α-diazoketones. 2-Methyl-1,5-diphenylpentane-1,3-dione **190** was initially employed as a model substrate to determine whether unsymmetrical α-diazoketones could be synthesised efficiently through this alternative procedure (**Scheme 2.96**). Equimolar amounts of β-diketone **190**, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and *p*-NBSA **166** in dichloromethane were used in this reaction with initial addition of β-diketone to the base prior to addition of the diazo transfer reagent. The reaction was found to be complete by infrared spectroscopic analysis following stirring at 0 °C for 1 h. These conditions were established following optimisation of this process by Ford.[167] Following purification by column chromatography, α-diazoketone **204** was isolated in 38% yield (not corrected for residual *p*-NBSA **166** present), which is comparable to Ford's work using Taber's conditions. Subsequently, Ford reported higher yields using modified conditions employing sodium hydride as base in place of DBU and replacing dichloromethane with THF. Proton and infrared spectroscopic properties were consistent with those reported in the literature[15] and obtained by Ford.[167]



Scheme 2.96

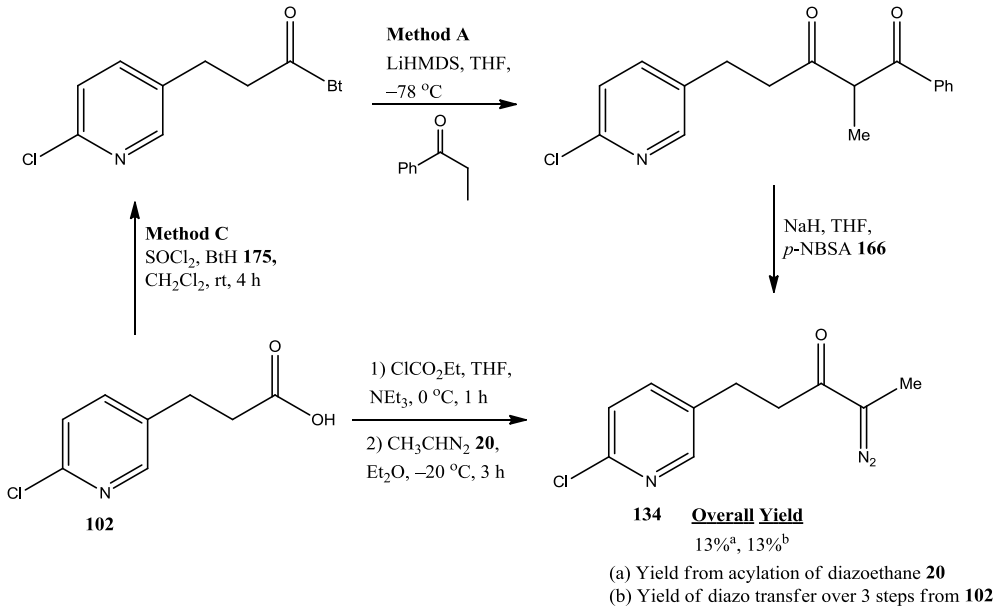
An important point is that the *p*-NBSA diazo transfer reagent **166** has a very similar retention factor (R_f) value to the α-diazoketone **204** and the azide was observed to co-elute on chromatography despite efforts to separate the components. In the infrared spectrum of **204**, the azide **166** was identified by a stretch at ν_{max} 2137 cm^{-1}, along with a characteristic α-diazoketone frequency at ν_{max} 2071 cm^{-1}. The characteristic signals for **166** were also recognised in the ^1H NMR spectrum of the purified product as doublets at δ_H 8.17 and 8.46 ppm. In order to ensure good separation of the azide reagent and the α-diazoketone **204**, the eluent of ethyl acetate/hexane was increased incrementally from (1:99) to (10:90) in purification by flash column chromatography. Even though this careful purification was followed, residual azide **166** was still present along with α-diazoketone **204**.

Diazo transfer to the halogenated pyridine β-diketones was next investigated employing the longer-chain β-diketone **196**. Using Ford's modified conditions of sodium hydride and THF, the α-diazoketone **134** was successfully prepared and isolated in 30% yield following column chromatography (**Scheme 2.97**). The spectroscopic characteristics obtained were identical to the sample of **134** synthesised *via* acylation of diazoethane. To the best of our knowledge, this is the first example of the successful preparation of a pyridine-containing internal α-diazoketone *via* Taber's debenzoylation diazo transfer approach. In addition, this illustrates for the first time in this work that pyridine containing α-diazoketones can be synthesised by the two routes.



Scheme 2.97

A comparison of the overall yields of α-diazoketone **134** obtained from the acylation of diazoethane and the diazo transfer method starting from the halogenated acid **102** is shown below (**Scheme 2.98**).

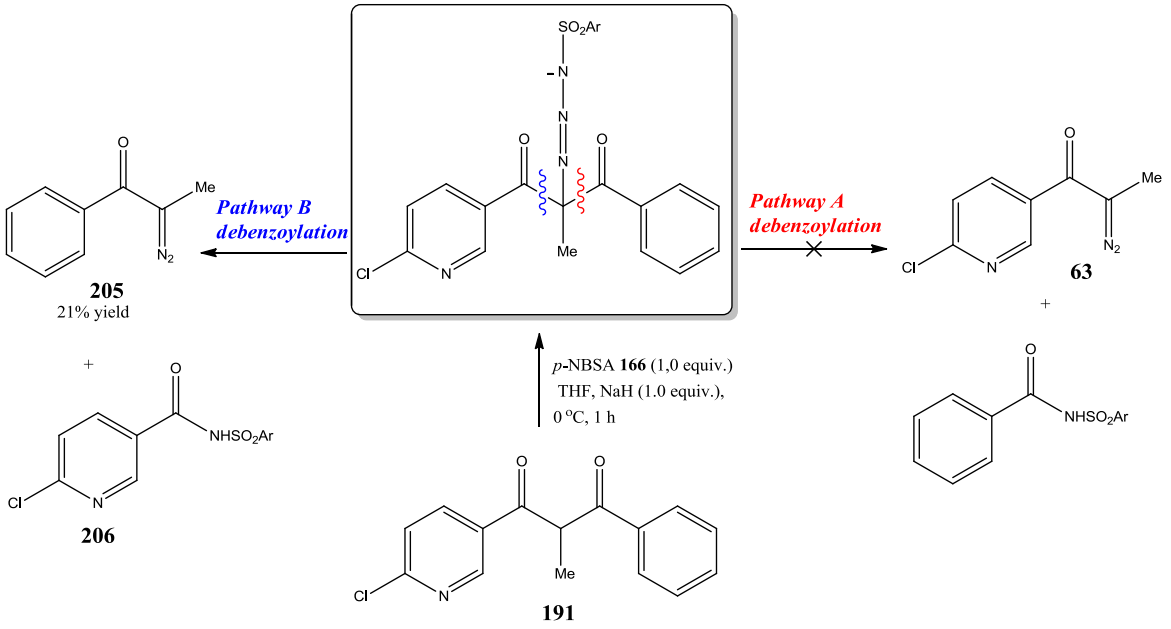


Scheme 2.98

For the synthesis of **134**, there appears to be no advantage for either method with respect to yields obtained as a 13% overall yield from carboxylic acid **102** was achieved in each case (**Scheme 2.98**). However, the 30% yield from the diazo transfer reaction leaves scope for improvement and provided this step can proceed more efficiently, there may be an advantage in the use of the three-step debenzoylation diazo transfer approach. The advantages of the diazo transfer route include avoiding the use of the hazardous reagent diazoethane **20** and the potential to extend the scope of the reaction to yield α-diazoketones with an alkyl group longer than a methyl through extending the ketones in the condensation step. However, the scale of the reaction remains limited through safety concerns relating to *p*-NBSA **166**.

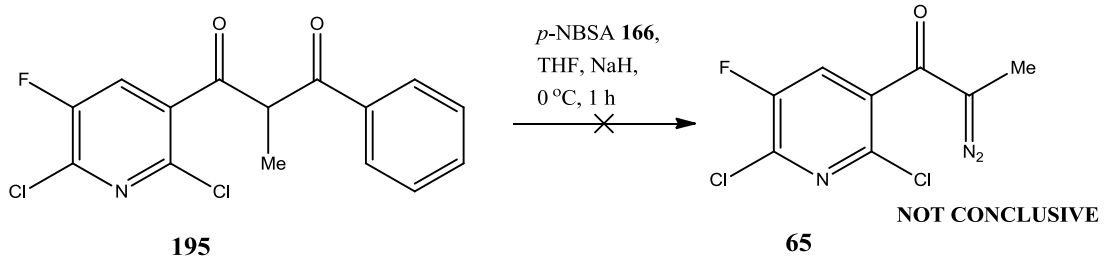
Further investigations of the debenzoylation diazo transfer focused on the analogous shorter-chain 6-chloro substituted diketone **191** using Ford's modified conditions (**Scheme 2.99**).[167] Following completion of reaction and purification by flash chromatography, the product was isolated as a bright yellow oil with characteristic stretches observed in the infrared spectrum at ν_{max} 2074 cm^{-1} and 2135 cm^{-1}, indicating both azide **166** and an α-diazoketone were present. However, the ^1H NMR spectroscopic data did not agree with sample of **63** prepared previously using the diazoethane acylation method.

On further inspection, the main component isolated from the attempted concomitant diazo transfer/debenzoylation procedure of **191** was 2-diazo-1-phenylpropan-1-one **205**, which was isolated in 21% yield (**Scheme 2.99**). The spectroscopic data for the isolated compound **205** were in good agreement with reported literature data.[208,209] The generation of α-diazoketone **205** can be rationalised by two competing debenzoylation pathways (A or B) with removal of the pyridoyl group favoured in this instance. The resulting sulfonamide **206** was not isolated. This issue was not previously encountered in work by Taber[168] or research in the Maguire group as the 1,3-diketones used as substrates for diazo transfer are not diaryl in nature, providing selective debenzoylation.[7,167]



Scheme 2.99

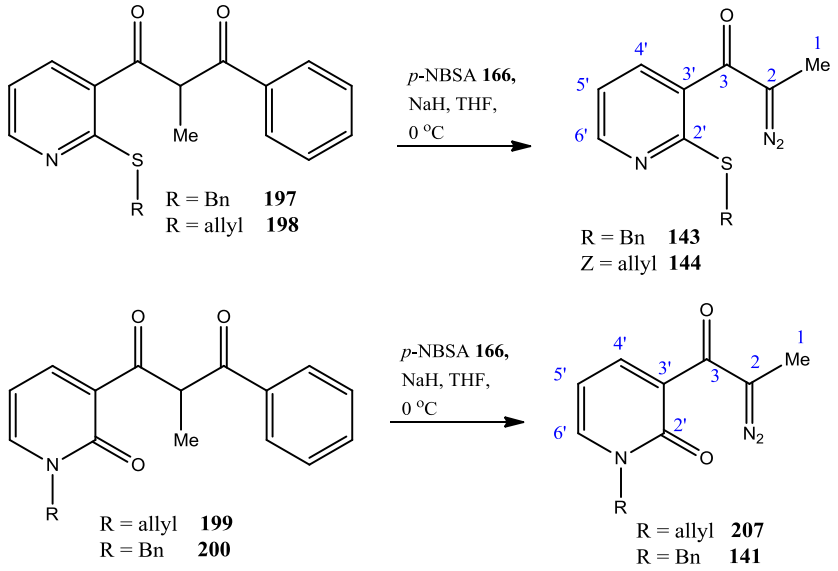
Diazo transfer was next attempted with 2,6-dichloro-5-fluoro substituted β-diketone **195**, where infrared spectroscopy of the crude product was indicative of the presence of an α-diazoketone (ν_{max} 2082 *cf.* 2081 cm^{-1} for acylation method earlier). However, following purification, only *p*-NBSA **166** and propiophenone (carried through from the condensation step) were recovered (**Scheme 2.100**).



Scheme 2.100

Finally, formation of α-diazoketones using tandem diazo transfer/debenzoylation methodology was attempted on the nitrogen and sulfur substituted β-diketones **197-200**. The results are summarised below (**Table 2.13**).

Table 2.13 *Isolated yields of 3-pyridine- and 3-pyridone-containing α-diazoketones* ***141***, ***143***, ***144*** *and* ***207*** *using diazo transfer*[a]



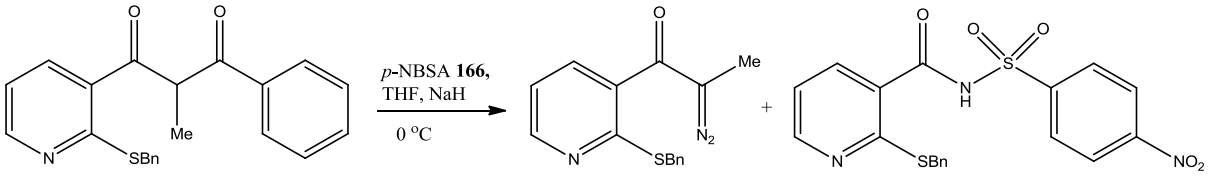
Entry	Diketone	Diazo	ν_{CO}/ cm^{-1}	ν_{CNN}/ cm^{-1}	Yield (%)[b]
1	**197**	**143**	1604	2080	6[c]+9 of **208**
2	**198**	**144**	1636[d]	2075[d]	–[e]
3	**199**	**207**	1654	2083	43
4	**200**	**141**	1652	2082	11[f]

[a] General reaction conditions consist of 1.0 equiv. of sodium hydride and 1.0 equiv.of *p*-NBSA **166** for entries 1-3.
[b] Isolated yield of product after column chromatography.
[c] Sample not isolated cleanly and seems to co-elute with some unreacted diketone **197** in a 1 : 1.9 ratio of **197** : **143.**
[d] Infrared spectroscopic analyisis of crude sample from attempted debenzoylation diazo transfer.
[e] Purified sample not identified but does contain an infrared streaching frequency at ν_{max} 2080 cm^{-1}.
[f] 2.0 equiv. of both sodium hydride and *p*-NBSA **166** used in this reaction.

Preparation of the α-diazoketones using this method was successful for the *N*-allyl compound **207** (**Table 2.13**, entry 3) and the *N*-benzyl compound **141** (**Table 2.13**, entry 4) in spite of the possibility of competitive debenzoylation as previously observed for synthesis of **63** *via* diazo transfer. This is the first preparation of the *N*-allyl α-diazoketone **207** in this work as this compound was not prepared by diazoethane acylation. The novel α-diazoketone **207** was characterised by infrared and ^{1}H NMR spectroscopy, as well as nominal and high resolution mass spectrometry. Analysis by ^{13}C NMR was not carried out for this compound as it was assumed at the time that the sample prepared was the *O*-allyl tautomer **140** that had already been characterised. Interestingly, the carbonyl stretch in the infrared spectrum of **207** was identified at ν_{max} 1654 cm^{-1}, in contrast to the absorption at ν_{max} 1604 cm^{-1} for the corresponding *O*-allyl tautomer **140**. In addition, spectral characteristics for *N*-benzyl compound **141** involving infrared (ν_{max} 1652 cm^{-1}) and proton NMR spectroscopy were in excellent agreement with data obtained earlier in this work using the diazoethane acylation method (see **Section 2.3.1.5.1**). Initial attempts employing diazo transfer on β-diketone **200** indicated formation of α-diazoketone **141**, as well as starting material **200**, which was isolated

as the major component. On repeating diazo transfer procedure for *N*-benzyl diketone **200**, an increase in the number of equivalents (2.0 equiv. *cf.* 1.0 equiv.) of both the base and the diazo transfer reagent was required for successful synthesis of α-diazoketone **141**. However, there was still some β-diketone **200** starting material isolated after purification.

However, debenzoylation diazo transfer methodology was much less efficient for the sulfur substituted β-diketones **197** and **198**. In a similar way to the preparation of *N*-benzyl α-diazoketone **141**, unreacted β-diketone starting material **197** was detected in the preparation of *S*-benzyl α-diazoketone **143** (**Table 2.13**, entry 1). This starting material was found to co-elute with α-diazoketone **143**, isolated as a bright yellow oil as the less polar fraction, while the more polar fraction was isolated as a white solid identified as **208** (**Scheme 2.101**). Although ^{1}H NMR and infrared (ν_{max} 2080 cm^{-1}) spectroscopic analysis of the yellow oil did indicate formation of the desired α-diazoketone **143** by comparison with substrate prepared *via* acylation method, this compound was not isolated cleanly. The mixture was observed in a 1.19 : 1 ratio of **197** : **143** after column chromatography, with the low yield obtained for this process artificially high due to the presence of co-eluting β-diketone **197**. The white solid gave signals which were tentatively assigned to the sulfonamide **208**, generated from cleavage at the carbonyl in α-position to the pyridine ring of β-diketone **197**.



Scheme 2.101

Preparation of the *S*-allyl α-diazoketone **144** (**Table 2.13**, entry 2) did initially appear to proceed sufficiently as determined by infrared spectroscopy, with a characteristic stretch at ν_{max} 2075 cm^{-1} detected in the crude sample. However, following purification, isolation of a sample of the α-diazoketone **144** was not achieved using diazo transfer methodology, despite the presence of a band at ν_{max} 2080 cm^{-1} for the purified product.

Thus, these synthetic endeavours illustrate that formation of unsymmetrical pyridine α-diazoketones *via* diazo transfer requires optimisation to make it a viable alternative to the diazoethane acylation method carried out earlier in this work (**Section 2.3.1.5**). Interestingly, competitive debenzoylation as observed in the preparation of **205** highlights the importance of linker chains on the 1,3-diketone precursors, enabling selective debenzoylation of the unsymmetrical 1,3-diketone. Accordingly, unsymmetrical 1,3-diketones would appear to be more suitable substrates for this approach. The scale on which these reactions can be conducted is limited by the amount of *p*-NBSA **166** that can be safely used in one reaction, though it offers a safer alternative for the preparation of these compounds than the conventional acylation protocol, circumventing the use of diazoethane **20**.

The three synthetic methods (acylation of diazoethane, debenzoylation diazo transfer and reaction of an acid chloride with EDA) employed to prepare α-diazoketones and α-diazo-β-ketoesters in this current investigation represent a considerable advancement in the scope of α-diazocarbonyl compounds bearing pyridine rings. The basicity of the lone pair of the ring nitrogen underpins much of the chemistry of pyridine and its derivatives and interestingly, it has been demonstrated that attenuating this effect permits generation of compounds whose synthesis was initially challenging. Allied to this, the work undertaken here has enabled a better understanding of the problems associated with such syntheses and may explain the dearth of literature precedent associated with formation of these compounds.

The next step in the investigation of these substrates was transition metal-catalysed transformations of pyridine α-diazocarbonyl compounds and examination of the products isolated from these reactions, as well as investigation of catalyst effects in these reactions.

2.4 Transition metal-catalysed transformations of pyridine-containing α-diazocarbonyl compounds and investigation of their reactivity

In this work, transition metal-mediated reactions of a series of novel pyridine α-diazoketones was carried out using rhodium(II) and copper(II) catalysis to explore the reactivity of the specific substrates. In this research, several reaction pathways were encountered: oxidation and subsequent formation of quinoxalines, 1,2-hydride shift, ylide formation/rearrangement and intermolecular cyclopropanation. Interestingly, C–H insertion and aromatic addition were not observed.

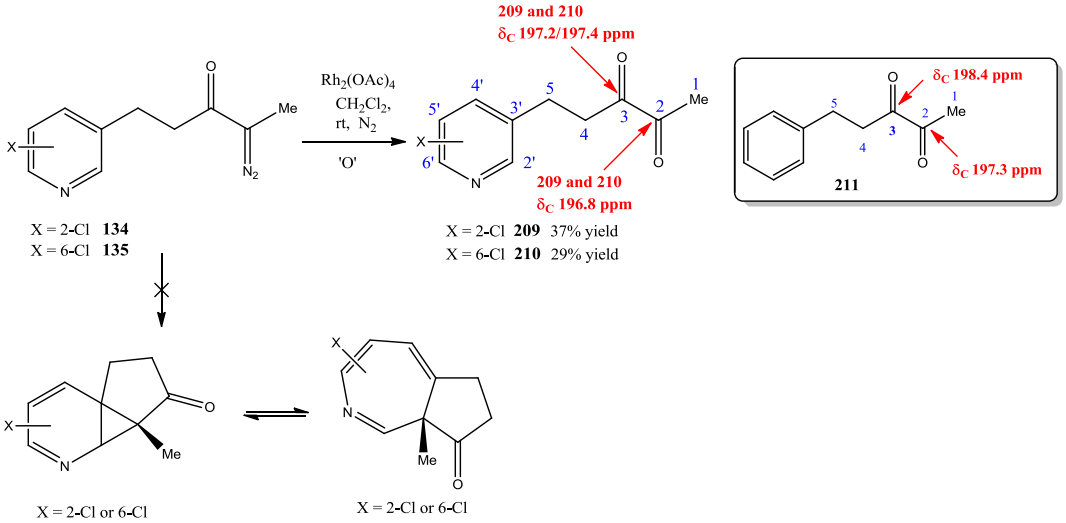
2.4.1 Oxidation of α-diazoketones to 2,3-diketones and subsequent formation of diazanaphthalenes (quinoxalines)

The original objective of this study was to explore if α-diazoketones such as **134** and **135** would undergo rhodium(II)-catalysed aromatic addition analogous to the work in the phenyl series (see **Section 2.2**). However, when the α-diazoketones **134** and **135** were exposed to $Rh_2(OAc)_4$ and dichloromethane under the conditions generally employed for aromatic addition, the principal product formed in each case unexpectedly proved to be the 2,3-diketones **209** and **210** respectively. At the outset of this work, one of the key questions was whether coordination of the pyridine to the transition metal catalyst would inhibit the standard reaction of the α-diazoketone to generate the rhodium carbenoid. The observed formation of the 2,3-diketones suggests that the pyridine alters the reaction pathway but does not appear to inhibit the catalysed transformation.

The formation of 2,3-diketones in transition metal-mediated reactions of α-diazoketones has previously been reported as a minor reaction pathway in the Maguire research group;[7,8,11,12] these compounds are believed to be generated *via* reaction of the metallocarbenoid with

molecular oxygen. The presence of water as an impurity can also result in the formation of side products, namely a glyoxal/α-hydroxyketone. The 2,3-diketone is generally viewed as an undesired side product in α-diazocarbonyl cyclisations and efforts were undertaken to prevent its formation. In our laboratory, Harrington and O'Keeffe previously conducted reactions using a Schlenk line to eliminate adventitious oxygen in α-diazoketone reactions.[10,17] In the present work, all glassware was flame-dried prior to use and dry nitrogen gas was bubbled through doubly distilled dichloromethane, for reactions at both at room temperature and at reflux for ~30 min before addition of the α-diazoketone. However, even with these safeguards, formation of the 2,3-diketones **209** and **210** was observed in all rhodium(II) acetate-catalysed reactions of α-diazoketones **134** and **135** (**Scheme 2.102**).

When the α-diazoketones **134** and **135** in dichloromethane were added dropwise to the rhodium catalyst in dichloromethane at room temperature under nitrogen, there was no noticeable colour change although there was evidence of nitrogen evolution, and monitoring by TLC and infrared spectroscopy showed complete disappearance of the α-diazoketones within 1 h at room temperature, indicating a very efficient reaction. Significantly, this suggests that the rhodium catalyst is not poisoned by pyridine in the reaction. On concentration, crude ^{1}H NMR and infrared spectra indicate that the major component is the 2,3-diketone which was a very unexpected outcome. Thus, a reaction pathway which had previously been identified as a minor reaction pathway in $Rh_2(OAc)_4$-catalysed reactions had now become the principal transformation. This can be rationalised in two ways: firstly, the presence of pyridine coordinates to the $Rh_2(OAc)_4$, thereby modifying the catalyst and leading to oxygenation, although later work involving spiking reactions with halogenated pyridines suggests this may not be the case (see **Section 2.4.3.2**) or alternatively, $Rh_2(OAc)_4$ reacts with the α-diazoketone to generate the rhodium carbenoid in a standard manner and the subsequent reaction of the carbenoid is modified by the presence of the pyridine leading to the oxygenation pathway.

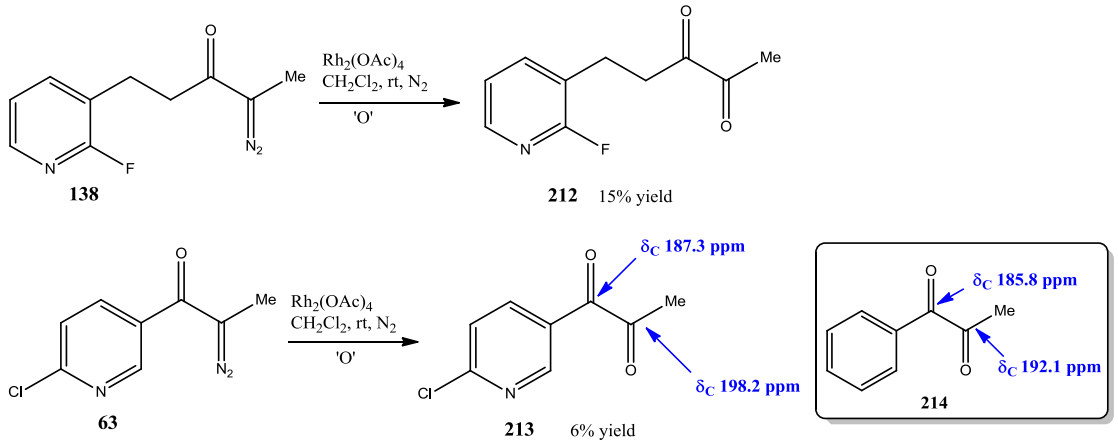


Scheme 2.102: ^{13}C NMR values (75.5 MHz, $CDCl_3$) and possible tentative assignment of carbonyl signals of 209 and 210 (based on comparison with assignment by Stas)[210]

Efficient formation of the 2,3-diketones in this work, despite the efforts taken to exclude oxygen and water was very unexpected and indicates that the transformation to the 2,3-diketone is a very favourable process.

The 2,3-diketones **209** and **210** formed by oxidation of α-diazoketones **134** and **135** were isolated as yellow oils after column chromatography. The 2,3-diketones were readily identified by infrared, ^{1}H and ^{13}C NMR spectroscopic analysis, as well as high resolution mass spectrometry. Analysis by infrared spectroscopy showed the disappearance of the diazo stretch at ν_{max} 2077 cm^{-1} and the emergence of a signal at ν_{max} ~1716 cm^{-1}, which was attributed to the 2,3-diketones. The presence of only one C=O signal in the infrared spectrum is a characteristic feature of α-diketones and is consistent with previously reported data in the Maguire group,[7,8,11] as well as literature values for compound **211** disclosed by Stas (ν_{max} 1711 cm^{-1})[210] and Conrow (ν_{max} 1710 cm^{-1}).[211] In the ^{1}H NMR spectrum, a distinctive singlet at δ_H 2.35 and 2.33 ppm for **209** and **210** respectively accounted for the three hydrogens of the methyl group, C(1)$\underline{H}_3$. In the ^{13}C NMR spectrum, the two carbonyl signals were seen at δ_C 196.8 and δ_C 197.2/197.4 ppm, corresponding to the diketone functionalities (**Scheme 2.102**). These carbonyl signals could be tentatively assigned as δ_C 197.4/197.4 ppm [$\underline{C}$(3)=O] and δ_C 196.8 ppm [$\underline{C}$(2)=O] by comparison with assignment for related phenyl 2,3-diketone **211** by Stas and co-workers who employed 2D HMQC and HMBC experiments to aid assignment of signals.[210] However, substrates in the current investigation would require additional 2D NMR experiments such as HSQC and HMBC to definitively assign both carbonyl signals for the 2,3-diketones **209** and **210**. Analysis by nominal and high resolution mass spectrometry was consistent with the molecular ion of the 2,3-diketones **209** and **210**. For example, in 2,3-diketone **209** the molecular ion was observed at $C_{10}H_{11}{}^{35}ClNO_2$ $[M+H]^+$ 212.0478 and $C_{10}H_{11}{}^{37}ClNO_2$ $[M+H]^+$ 214.0464 and the chlorine isotope pattern was observed in both the nominal and high resolution mass spectra. Having proposed **209** and **210** as the 2,3-diketones, their structure was confirmed by condensation of **209** and **210** with 1,2-diaminobenzene (see **Scheme 2.106**).

Having identified diketone formation as a significant reaction pathway with α-diazoketones **134** and **135**, the fluorine substituted 2,3-diketone **212** was also prepared from oxidation of α-diazoketone **138** and isolated following column chromatography while the yield was substantially lower than for the chlorine substituted derivatives **209** and **210**. However, only ^{1}H NMR and infrared spectroscopic analysis was carried out on this compound. In addition, the spectral features of the product isolated from an earlier rhodium(II)-catalysed transformation of **63** resulted in identification of 2,3-diketone **213**, which was isolated in low yield following chromatography (**Scheme 2.103**). Interestingly, the two carbonyl signals were located at δ_C 187.3 and 198.2 ppm in the ^{13}C NMR spectrum of **213**, compared to δ_C 196.8 and 197.2/197.4 ppm in the ^{13}C NMR spectrum of **209** and **210**. The disparity between the signals for conjugated and unconjugated 2,3-diketones correlated well with related benzene analogue **214** reported in the literature, although conclusive assignment of $\underline{C}$(2)=O and $\underline{C}$(3)=O was not described by Stergiou and co-workers.[212] Thus, the assignment of the carbonyl signals in the present work remains tentative.



Scheme 2.103

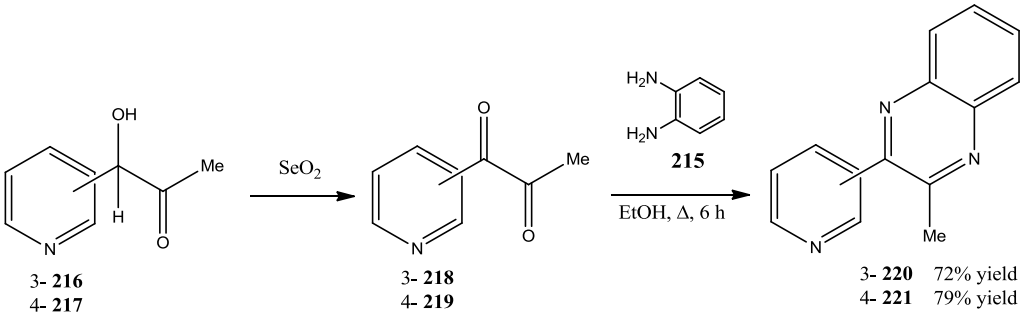
Having established formation of 2,3-diketones as the main reaction pathway in these carbenoid-mediated processes, subsequent work involved deliberate generation of 2,3-diketones from transformations of α-diazoketones **63-65**, **136**, **137**, **139** with the reactions conducted under air instead of nitrogen. However, in these cases, the 2,3-diketones were not purified and instead brought through crude to prepare the corresponding quinoxalines, after initial confirmation by ^{1}H NMR and infrared spectroscopy on the reaction mixture following concentration.

Previous work in our research group reported generation of phenyl-substituted 2,3-diketones from α-diazocarbonyl transformations using rhodium catalysts, with these compounds isolated as side products in low yield,[7,8,11,12] Subsequently, the 2,3-diketones were characterised as the corresponding diazanaphthalenes (quinoxalines) following condensation with 1,2-diaminobenzene **215**. While the generation of diketones from reactions of α-diazoketones is well-precedented utilising peroxy acids,[213] *t*-butylhypochlorite,[214] ozone[215] and DMD as oxidising agents,[29,216-219] direct conversion of α-diazoketones to diketones without use of an oxidising agent has not been published to the best of our knowledge. However, this reaction pathway has been reported previously in our research group.[7,8,11,12]

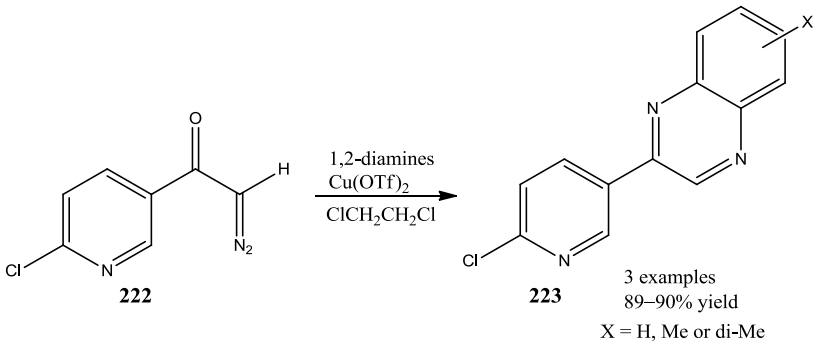
Quinoxaline derivatives possessing a pyrazine motif display an impressive range of biological and therapeutic properties encompassing antiviral, antibacterial,[220,221] antiprotozoal, anti-inflammatory and anticancer activity.[222-225] Other applications of these benzodiazines include use as dyes,[226] chemically controllable switches,[227] electroluminescent materials[228] and organic semiconductors.[226]

In 1980, Knaus reported formation of pyridine-containing quinoxalines **220** and **221** by condensation of 2,3-diketones **218** and **219** with 1,2-diaminobenzene **215** (**Scheme 2.104**).[229] The 2,3-diketones were prepared from selenium dioxide oxidation of pyridyl α-hydroxyketones **216** and **217** in the previous step. More recently, Yadav has proffered a one-pot preparation of quinoxalines **223** from terminal α-diazoketones and 1,2-diamines using copper(II) triflate (**Scheme 2.105**).[230] Using this newly-developed method, the quinoxalines

were synthesised in excellent yields from the one-pot reaction of the α-diazoketones. While this is the only report for 6-chloro substituted terminal α-diazoketone **222** in the literature, no spectroscopic data or experimental preparation is described for this compound. Notably, the authors do not mention formation of the ketoaldehyde as an intermediate.



Scheme 2.104: Quinoxalines reported by Knaus[229]



Scheme 2.105: Quinoxalines reported by Yadav[230]

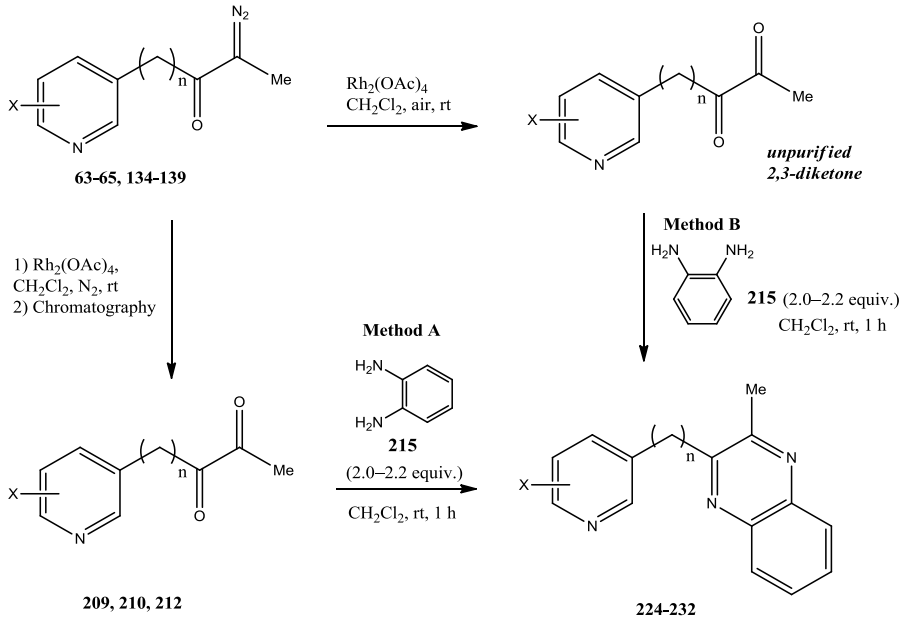
From earlier work in our group, preparation of the quinoxalines is usually conducted under mild conditions using dichloromethane at room temperature and the reaction mixture stirred for 1 h. 1,2-Diaminobenzene **215** was freshly purified by recrystallisation from hot dichloromethane using the procedure carried out by McNamara,[11] followed by treatment with charcoal and a hot filtration (method originally described by Sanchez[231]). Prior to this, Buckley purified 1,2-diaminobenzene **215** by hot recrystallisation from a saturated solution of sodium dithionate. Buckley had previously reported isolation of 2,3-diketones by chromatography and subsequent reaction with 1,2-diaminobenzene **215** to yield the quinoxalines.[8] Furthermore, she reported an *in situ* method in which the α-diazoketone is firstly reacted with the rhodium catalyst followed by addition of 1,2-diaminobenzene **215** without isolation of the 2,3-diketone intermediate. Best results were obtained using $Rh_2(cap)_4$, which is a relatively inefficient catalyst for aromatic addition. In general, the *in situ* approach where 1,2-diaminobenzene **215** is added subsequent to the α-diazoketone reaction is a very efficient method of definitively identifying 2,3-diketone as a reaction byproduct. This is particularly useful as in our experience, recovery of 2,3-diketones following chromatography is relatively poor.

In this project, the quinoxalines were synthesised by two methods;

- Method A: Isolation of the 2,3-diketone by chromatography and condensation with 1,2-diaminobenzene **215** used with **134**, **135** and **138** or,

- Method B: Generation of 2,3-diketone without purification and subsequent condensation with **215** used with **63-65**, **136**, **137** and **139**.

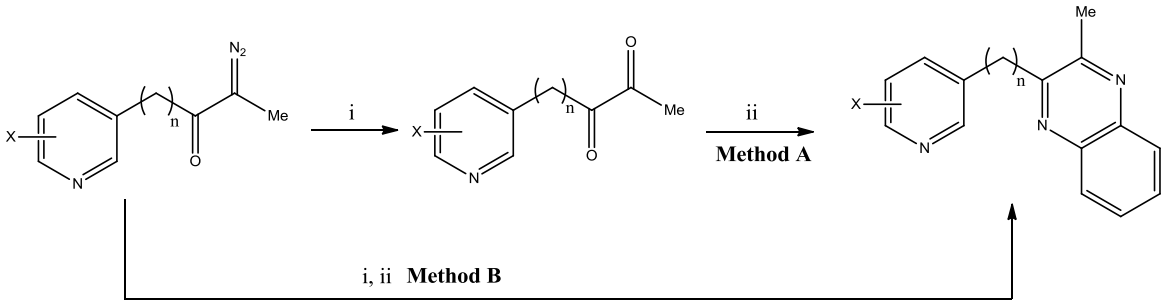
Method B was conducted as follows; a solution of the α-diazoketone in dichloromethane was added dropwise to the $Rh_2(OAc)_4$ (1 mol%) at room temperature under air. Infrared and TLC monitoring demonstrated complete disappearance of the α-diazoketones within 1 h. Concentration of the reaction mixture followed by ^1H NMR and infrared spectroscopy confirmed presence of 2,3-diketones as the principal reaction products. The crude mixture was immediately redissolved in dichloromethane and 1,2-diaminobenzene **215** was added directly and the reaction mixture stirred for 1 h at room temperature followed by concentration to yield the quinoxalines, each of which was purified by chromatography. At no stage during this work was the 1,2-diaminobenzene added directly to the α-diazoketone/$Rh_2(OAc)_4$ mixture. The generation of quinoxalines by Methods A and B is shown below (**Scheme 2.106**).



Scheme 2.106: Preparation of pyridyl quinoxalines 224-232 *via* Methods A and B

The particular method used in the preparation of quinoxalines **224-232**, as well as isolated yields and melting points is summarised below (**Table 2.14**).

Table 2.14 *Isolated yields and melting points of quinoxalines* ***224-232*** *using Methods A and B*



i $Rh_2(OAc)_4$, CH_2Cl_2, air, rt
ii 1,2-diaminobenzene **215**, CH_2Cl_2, rt, 1 h

Entry	X =, *n* =	Diazo	Diketone	Quinoxaline	m.p. (°C)	Yield (%)[a] Method A[a]	Method B[b]
1	2-Cl *n* = 0	**64**	–	**224**	149–150	–	70
2	6-Cl *n* = 0	**63**	–	**225**	184–185	–	58
3	2,6-Cl_2,5-F *n* = 0	**65**	–	**226**	137–139	–	48
4	2-Cl *n* = 2	**134**	**209**	**227**	136–138	54 (37)	–
5	2-F *n* = 2	**138**	**212**	**228**	118–119	quant. (15)	–
6	2-OMe *n* = 2	**139**	–	**229**	71–72	–	50
7	6-Cl *n* = 2	**135**	**210**	**230**	118–120	56.(29)	–
8	2,6-Cl_2 *n* = 2	**136**	–	**231**	103–105	–	63
9	2-Br *n* = 2	**137**	–	**232**	115–117	–	43

[a] Isolated yield of quinoxaline following chromatography, using Method A; condensation of pure 2,3-diketone with 1,2-diaminobenzene **215**. The figure in parentheses is the yield of diketone isolated from oxidation of the α-diazoketone.

[b] Isolated yield of quinoxaline following chromatography, using Method B; $Rh_2(OAc)_4$-catalysed reaction of α-diazoketone to generate the 2,3-diketone without purification followed by condensation with 1,2-diaminobenzene **215.**

The pyridine-substituted quinoxalines **224-232** were prepared in moderate to good yields and full characterisation was carried out on each of these novel compounds. In accordance with results previously reported by Buckley,[8] the yield of quinoxalines obtained directly from α-diazoketones (Method B *via* the 2,3-diketone intermediate) were higher in all instances than the yield of the isolated 2,3-diketones (**Table 2.14**, figures in parentheses), illustrating the inefficiency of the 2,3-diketone isolation. Thus, Method B is a more efficient synthetic route than Method A towards the preparation of pyridine-containing quinoxalines. Analysis by ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, melting point, nominal mass spectrometry and high resolution mass spectrometry were all consistent with the formation of the quinoxalines. Accurate elemental analysis was successful for quinoxalines **224-226** where the pyridine ring is directly linked to the quinoxaline but not for quinoxalines **227-232** with the two carbon linkers. The general numbering scheme of conjugated and unconjugated pyridyl quinoxalines is shown below (**Figure 2.36**).

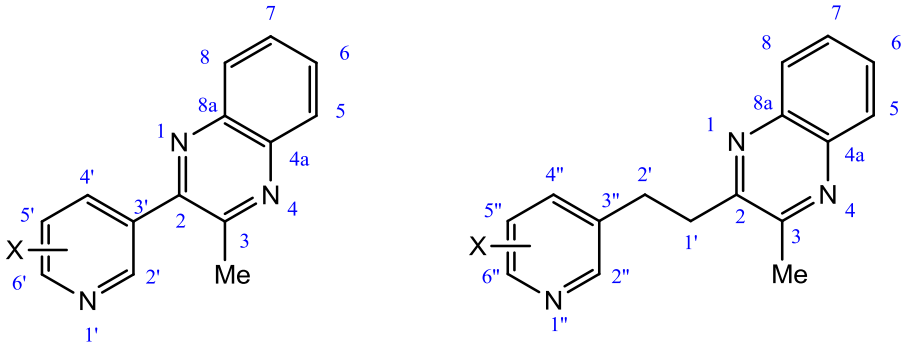


Figure 2.36: Numbering Scheme for conjugated and unconjugated pyridyl diazanaphthalenes (quinoxalines)

The most characteristic signal in the ^{1}H NMR spectrum of the diazanaphthalenes is the singlet at δ_H ~2.73 ppm attributed to the aryl methyl group, C(3)C$\underline{H}_3$, which has shifted from value of δ_H ~2.35 ppm for the 2,3-diketone precursors. A characteristic overlapping of the two methylene groups as a multiplet, integrating for four hydrogens, is observed for some of the longer-chain derivatives at *ca*. δ_H 3.32 ppm (**Figure 2.37**). In addition, complex multiplets correlating for the aromatic signals of the quinoxaline ring are seen at δ_H ~7.63–7.73 and ~7.96–8.03 ppm (series with linker chain **227-232**) and δ_H ~7.74–7.89 and ~8.06–8.14 ppm (series where pyridine ring is directly linked to the quinoxaline **224-226**) (**Figure 2.37**). It is observed that the multiplets for the aromatic signals are located at ~0.1 ppm further downfield for the conjugated analogues than their counterparts possessing the linker chains. The ^{13}C NMR spectrum also showed some characteristic signals with the four aromatic $\underline{C}$–H signals seen at δ_C ~128.3, 128.5, 128.9, 129.2 ppm for $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H and, $\underline{C}$(8)H. The other characteristic peaks in the ^{13}C NMR spectrum were the two bridgehead carbons which appeared as two very close signals at δ_C ~140.9 and 141.0 ppm.

Each of the quinoxalines was isolated as as a yellow/brown solid and the melting points obtained for these solids were typically in the range of between 100–140 °C, with exceptions of **225**, which had a higher melting point of 184–185 °C and the methoxy substituted compound **229**, which had a lower value of 71–72 °C (**Table 2.14**, entries 2 and 6). Interestingly, the quinoxaline formation is equally efficient for both series with and without the linker chain. Furthermore, the reaction efficiency appears to be insensitive to the nature of substituents on the pyridyl ring. For synthetic purposes, Method B leads to higher overall yields avoiding the purification of the intermediate 2,3-diketones.

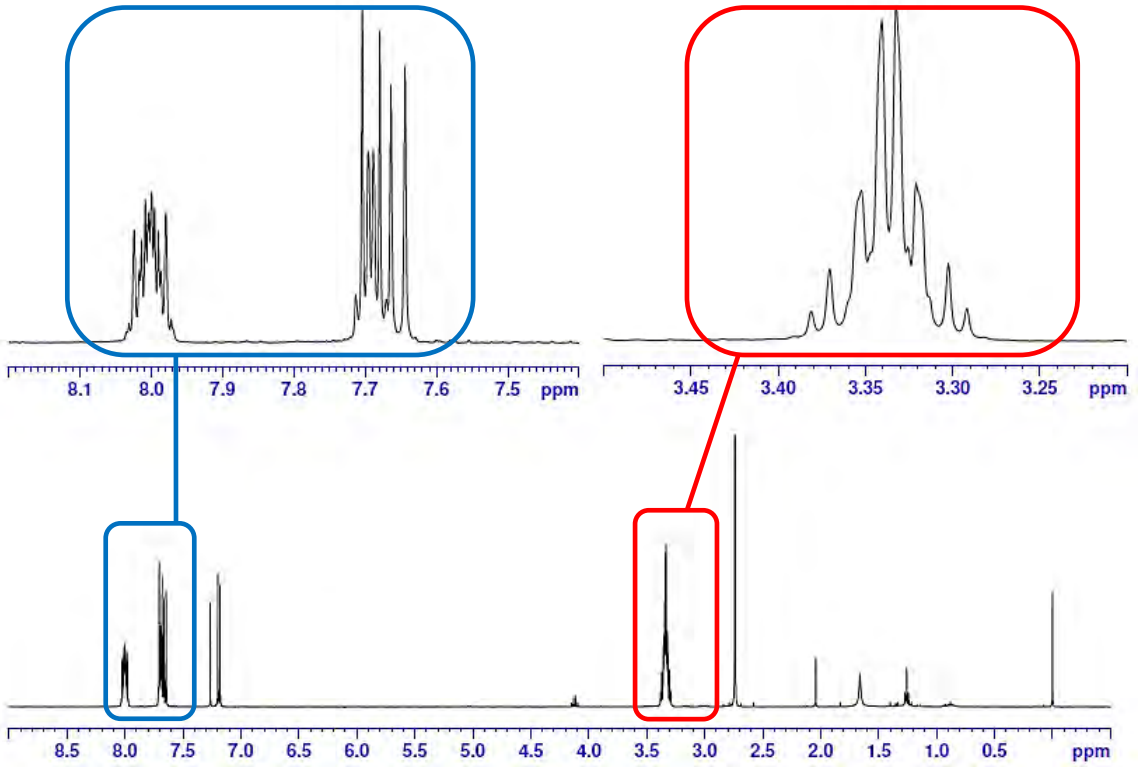
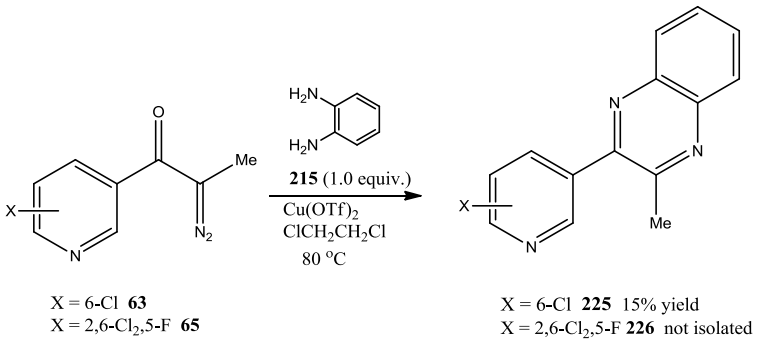


Figure 2.37: ^{1}H NMR (400 MHZ, $CDCl_3$) spectrum and expansion of characteristic signals for C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$ as well as the aromatic signals C(5)$\underline{H}$–C(8)$\underline{H}$ for quinoxaline 231

It should be noted that preparation of quinoxalines using the copper-catalysed one-pot procedure outlined by Yadav *et al.* for terminal α-diazoketones (see **Scheme 2.105**) was attempted in this work using internal α-diazoketones **63** and **65** (**Scheme 2.107**).[230] Using the conditions developed by Yadav,[230] generation of quinoxalines **225** and **226** was variable and at best poorly efficient. Successful formation of an impure sample of **225** was achieved in 15% yield following column chromatography and the spectroscopic data were consistent with data obtained for **225** using Method B above. However, in the preparation of **226**, TLC analysis of crude sample displayed a complex mixture of products and no purification was carried out on this substrate.



Scheme 2.107

It is clear that the rhodium-mediated generation of the quinoxaline is far preferable than the copper-mediated process. Furthermore, the rhodium-catalysed process is undertaken at at room temperature while the Yadav procedure was conducted at 80 °C.[230] It is reasonable to suggest that adventitious oxygen may be involved in formation of a non-isolated 1,2-dicarbonyl as an intermediate in Yadav's work, although this is not discussed in their report.

In this work, two X-ray crystal structures were obtained for quinoxalines **227** and **232** (grown from $CDCl_3$) and these structures are shown below (**Figures 2.38** and **2.39**) confirming the formation of these heterocyclic systems. Interestingly, the two structures are essentially identical despite replacement of the chlorine with the larger bromine atom. Each of the crystal structures of **227** and **232** displayed the same intermolecular interactions: two weak methyl C–H···N interactions at ~2.70 Å are observed, as well as a π···π interaction due to the close proximity (~3.62 Å) of the two double bonds C(2) and C(3). The dihedral angles between C3"-C2'-C1'-C2 for **227** and **232** were observed as 172.0° and 170.8° respectively, illustrating a deviation in planarity due to packing constraints.

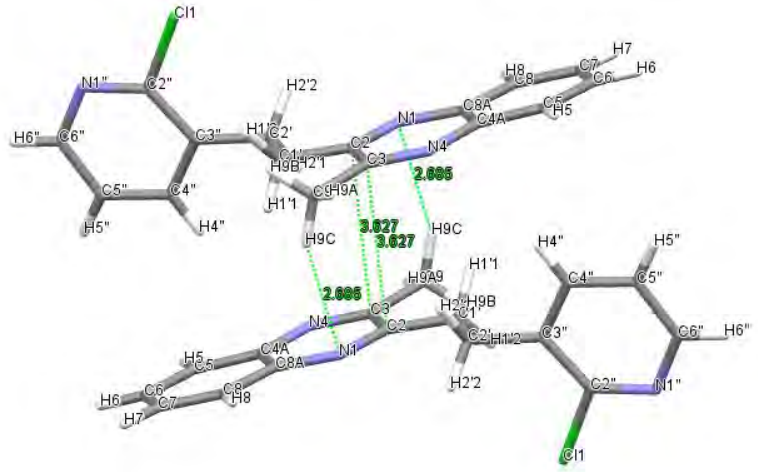


Figure 2.38: X-ray crystal structure of 227

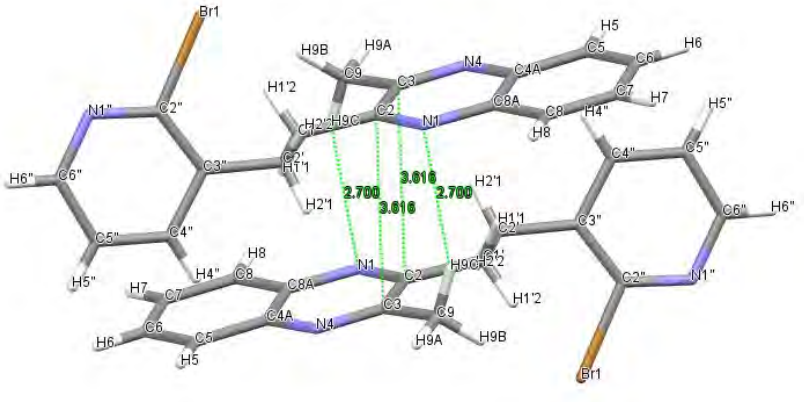


Figure 2.39: X-ray crystal structure of 232

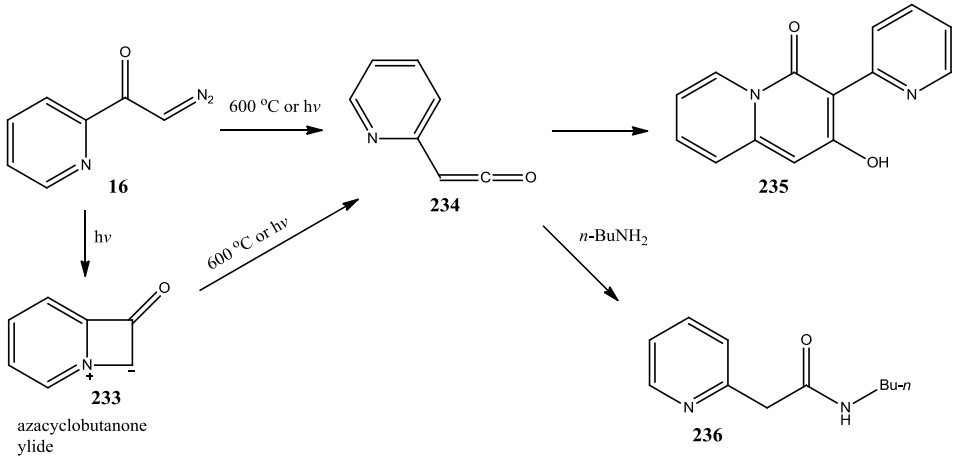
In conclusion, unexpected formation of the 2,3-diketones proved to be the principal reaction pathway in the rhodium(II)-catalysed reactions of the pyridyl α-diazoketones even when the reactions were conducted under nitrogen.

2.4.2 Transformations of pyridine α-diazoketones under Schlenk conditions

2.4.2.1 Background

Since transition metal-catalysed transformations of pyridine α-diazoketones under standard cyclisation conditions resulted in formation of 2,3-diketones, *via* reaction of the metallocarbenoid with molecular oxygen, attention next focused on investigation of whether carrying out the same reactions under Schlenk conditions would have an impact on the product distribution. The stringent elimination of oxygen from the reaction was anticipated to lead to a variation in reaction outcome, resulting in alternate pathways which are not seen in the presence of oxygen.

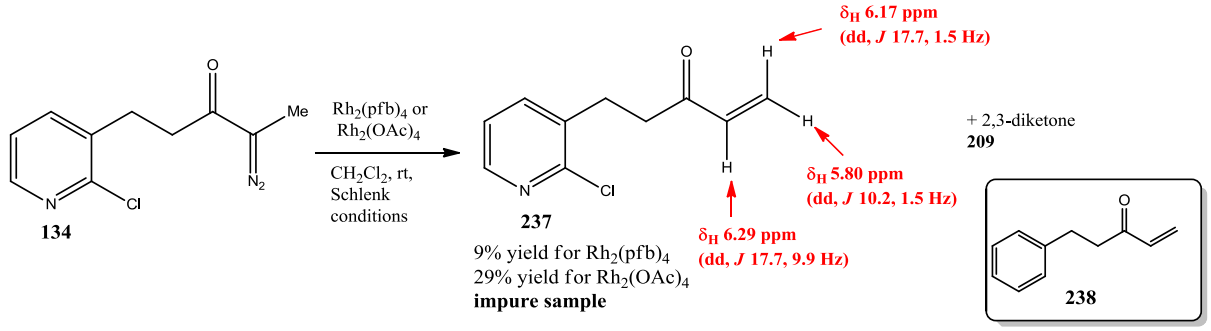
Alternative reaction outcomes of pyridine-containing α-diazoketones other than oxidation have been previously described by Wentrup,[69] Tidwell,[232,233] Oku[34] and Padwa.[143] Wentrup has carried out photolytic reaction of pyridine α-diazoketone **16** to lead to the formation of azacyclobutanone ylides (**Scheme 2.108**).[69] This process is favoured due to the availability of the lone pair on the nitrogen and its proximity to the photolytically-generated electron-deficient carbene. The azacyclobutanone/azomethine ylide **233** can be further heated or undergo flash vacuum pyrolysis in an argon matrix to generate a ketene intermediate **234** *via* Wolff rearrangement. Additional transformations of **234** can result in dimerisation to afford **235** as investigated by Wentrup[69] or Arndt-Eistert homologation of the ketene with an amine to furnish the amide **236** as demonstrated by Tidwell.[233] Design of substrates containing a diazo moiety adjacent to the nitrogen lone pair has also been utilised by Oku[34] and Padwa.[143] These reactive azomethine ylides were subsequently used in 1,3-dipolar cycloadditions generating cycloadducts (see **Section 2.3.1**). Interestingly, Padwa used $Rh_2(OAc)_4$ to generate the azomethine ylides while Oku employed $Cu(hfacac)_2$ as catalyst.



Scheme 2.108: Reactions of pyridine substituted α-diazoketones

2.4.2.2 Cyclisations of pyridyl α-diazoketones under Schlenk conditions

The rhodium(II)-mediated reactions of pyridine-containing α-diazoketones **134** and **135** were carried out using Schlenk conditions in an attempt to prevent the oxygenation pathway, providing some interesting observations. Transition metal-catalysed transformations of **134** in the presence of either rhodium(II) acetate or rhodium(II) perfluorobutyrate at room temperature furnished a very complex reaction mixture as determined by TLC analysis from which a fraction was isolated by chromatography containing two components; the 2,3-diketone **209** in addition to a new product, enone **237** [ratio of **237** : **209** is 57 : 43 for $Rh_2(pfb)_4$ reaction and ratio of **237** : **209** is 78 : 22 for $Rh_2(OAc)_4$ reaction] (**Scheme 2.109**). The structural assignment of **237** is based on identification of characteristic terminal alkene signals of the enone in the ^{1}H NMR spectrum while characteristic signals for 2,3-diketone **209** were in agreement with those obtained earlier in this work (see **Section 2.4.1**). It is noteworthy that a pink colour was observed in the reaction mixture following addition of the α-diazoketone **134** in dichloromethane to the $Rh_2(pfb)_4$/dichloromethane mixture, while no noticeable colour change was observed following addition of the α-diazoketone **134** to the $Rh_2(OAc)_4$/dichloromethane mixture.

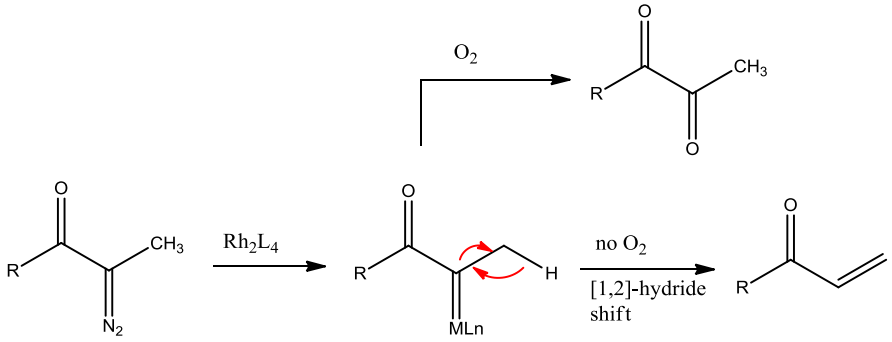


Scheme 2.109

Characteristic signals for the enone moiety of **237** in the ^{1}H NMR spectrum were observed as doublets of doublets at δ_H 5.80 (*J* 10.2, 1.5 Hz), δ_H 6.17 (*J* 17.7, 1.5 Hz) and δ_H 6.29 (*J* 17.7, 9.9 Hz) ppm, as highlighted in **Scheme 2.109**. The aromatic peaks on the pyridine ring of the enone **237** completely overlapped with the corresponding signals for the 2,3-diketone **209**. Further overlap between methylene groups of enone **237** and C(4)$\underline{H_2}$ methylene group of the 2,3-diketone **209** was also observed. The chemical shifts and coupling constants obtained for enone **237** were in good agreement with ^{1}H NMR spectral data described for the phenyl analogue **238** by Zhang and co-workers;[234] δ_H 2.90–2.99 (m), 5.84 (dd, *J* 10.4, 1.2 Hz), 6.22 (dd, *J* 17.6, 1.2 Hz), 6.36 (dd, *J* 17.6, 10.4 Hz) ppm.

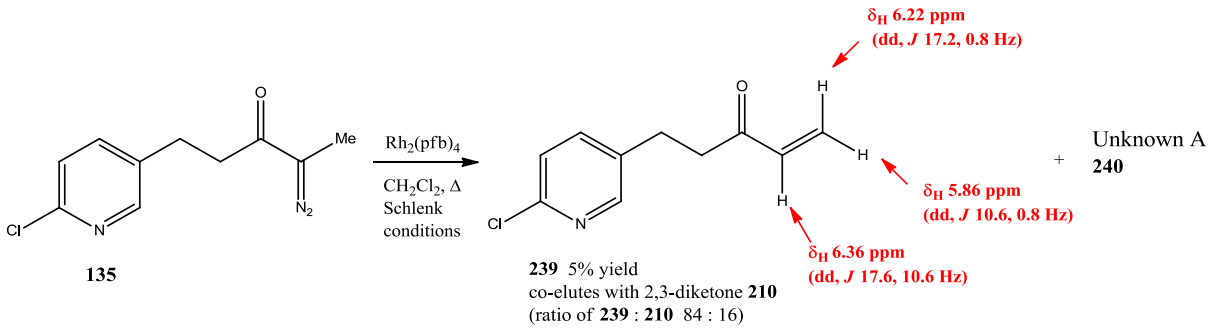
It is believed the enone **237** is formed by a 1,2-hydride shift in the carbenoid (**Scheme 2.110**). The key observation that the crude reaction mixture is much more complex when the rhodium(II)-catalysed transformation is conducted under Schlenk conditions provides mechanistic insight. Thus, the rhodium catalyst reacts with the α-diazoketone to generate the rhodium carbenoid. In the presence of oxygen, by far the most favourable reaction pathway is

oxygenation to yield the 2,3-diketones, as evidenced by the relatively clean crude products when the reactions were conducted under air. Under Schlenk conditions, where the carbenoid cannot react with oxygen, a myriad of less favourable reaction pathways compete leading to a very complex crude reaction product. Among these, the 1,2-hydride shift is the sole pathway identified due to the very characteristic signals for the terminal enone.



Scheme 2.110

The α-diazoketone **135** was treated with $Rh_2(pfb)_4$ under both reflux conditions and at room temperature, with both reactions conducted under Schlenk conditions (**Scheme 2.111**). The reaction which was carried out under reflux conditions yielded the enone **239** arising from a 1,2-hydride shift which co-eluted with a small amount of the 2,3-diketone **210** as the only identifiable components albeit in very low yield (ratio of **239** : **210** is 84 : 16). An Unknown A **240** was isolated as the major product. ^{1}H NMR spectroscopy of **239** provided values which were consistent to those obtained above for enone **237** (**Scheme 2.109**). Nominal and high resolution mass spectrometry of 1,2-hydride shift product **239** were also consistent with the generation of this compound. The signals for unknown A **240** could speculatively be ascribed to an O–H insertion product from a characteristic signal at δ_H 1.34 ppm (d, *J* 7.2 Hz); however, there is no definitive evidence of formation of this compound. On carrying out reaction of **135** under Schlenk conditions at room temperature, the 2,3-diketone **210** was identified as the major isolated product providing identical spectroscopic characteristics to those obtained earlier (see **Section 2.4.1**).



Scheme 2.111

In the figure below (**Figure 2.40**), the characteristic signals for each compound following chromatography are highlighted; peaks for the enone **239** are identified by the red region, peaks for Unknown A **240** by the blue region and peaks for 2,3-diketone **210** by the green

region. In addition, the same determination of signals is used in **Figure 2.41** below where the peaks ascribed to the enone **239** are highlighted by the red region while the peaks for the 2,3-diketone **210** are identified by the green region.

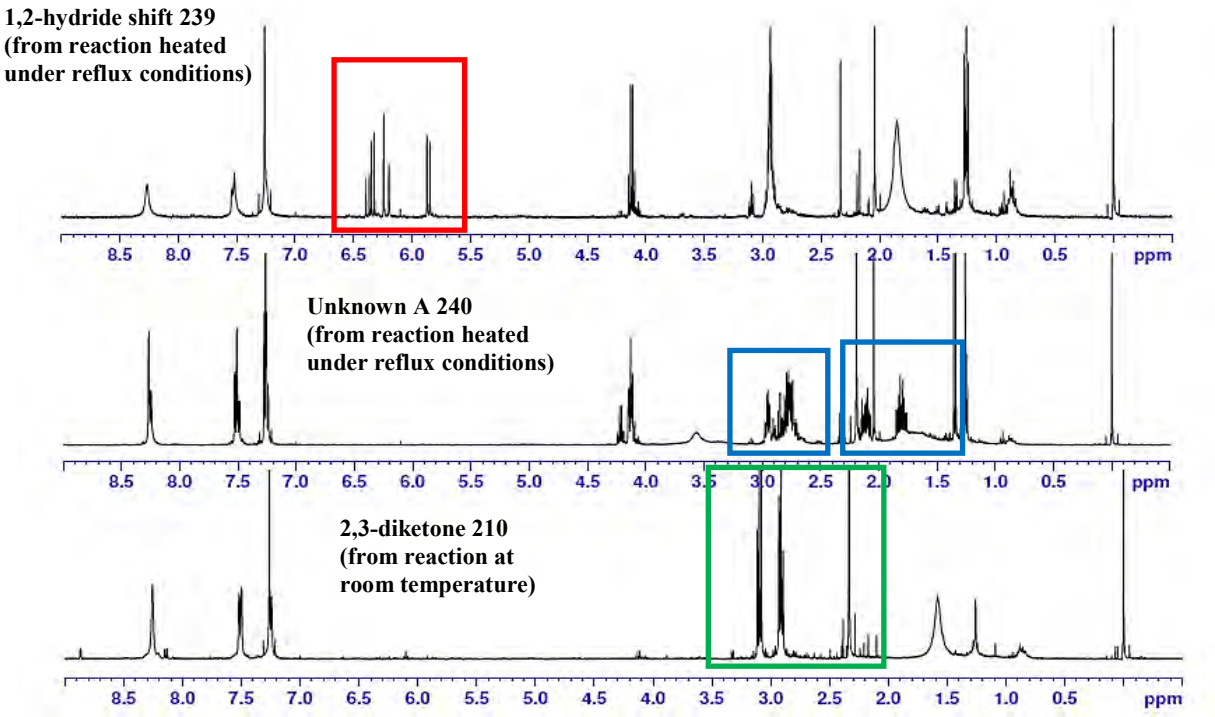


Figure 2.40: ^{1}H NMR (400 MHZ, $CDCl_3$) spectra of 210, 239 and 240 after chromatography

Figure 2.41 compares the ^{1}H NMR spectra of the crude products from the reaction of α-diazoketone **135** with $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ under nitrogen or under Schlenk conditions. Using $Rh_2(OAc)_4$ under nitrogen, the crude product consists predominantly (>80%) of the 2,3-diketone **210**. The same reaction conducted in a Schlenk line with $Rh_2(OAc)_4$ results in a much more complex crude ^{1}H NMR spectrum with clear evidence of terminal enone **239** in addition to 2,3-diketone **210**. Use of $Rh_2(pfb)_4$ under Schlenk conditions again provides a complex mixture but in this case with an increased proportion of the 1,2-hydride shift product enone **239**, consistent with use of the more electronegative $Rh_2(pfb)_4$ catalyst.

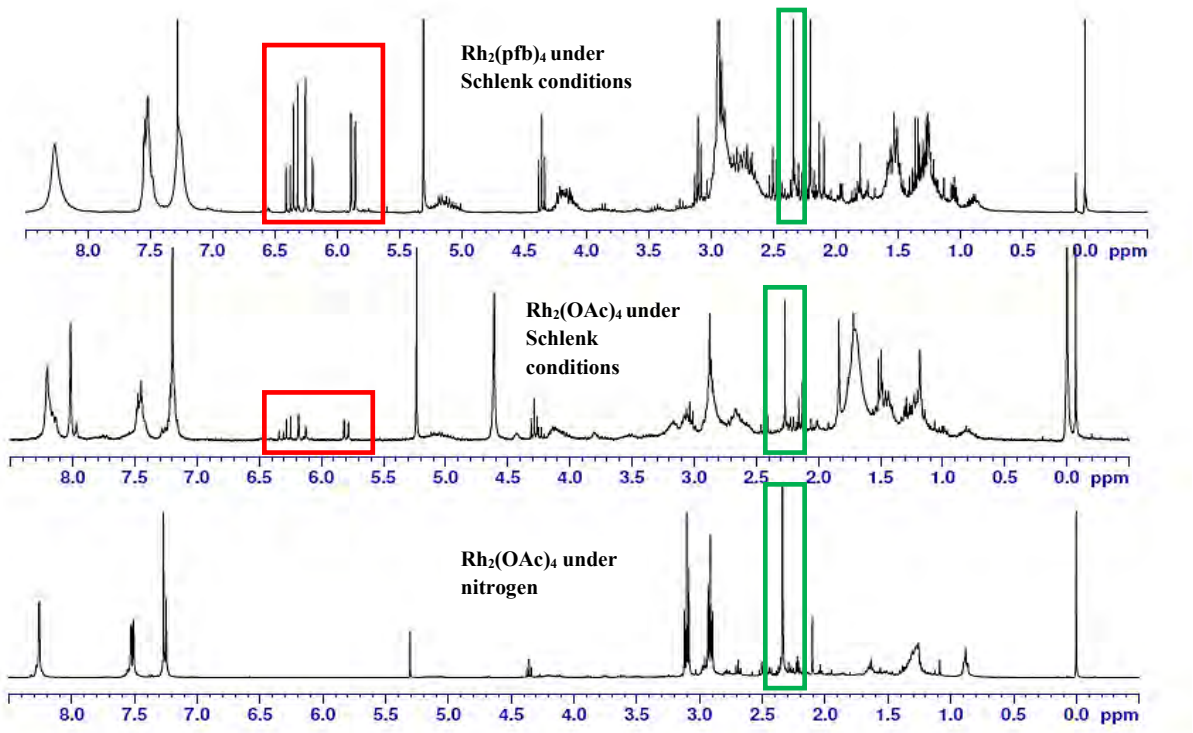
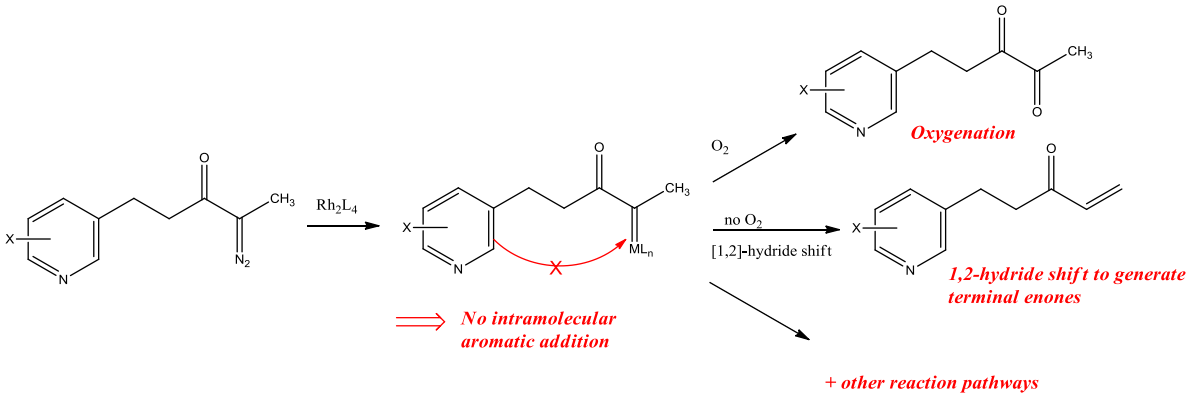


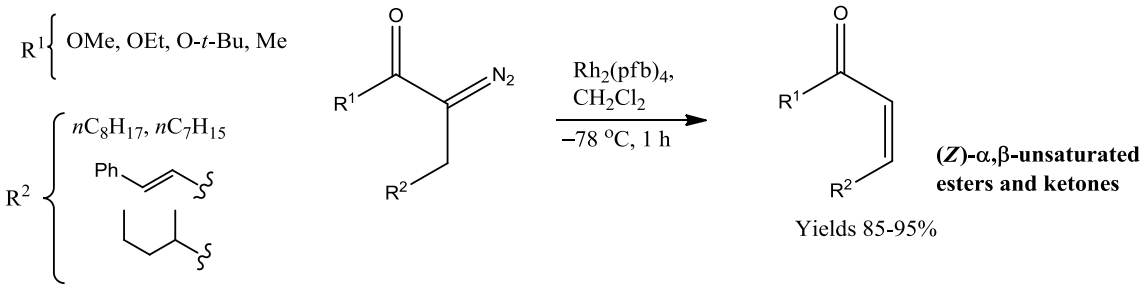
Figure 2.41: Crude ^{1}H NMR spectra from reactions of 135 in the presence of $Rh_2(OAc)_4$ or $Rh_2(pfb)_4$ under nitrogen or conducted under Schlenk conditions, (300 MHz, $CDCl_3$) for top two spectra and (400 MHz, $CDCl_3$) for bottom spectrum

The formation of enones **237** and **239** *via* 1,2-hydride shift represents a very interesting and unanticipated reaction pathway. While the research team has worked with the analogous phenyl substituted α-diazoketones for many years, the analogous 1,2-hydride shift products have not been seen other than a single isolated report by O'Keeffe which reported formation of the terminal enone as a minor component in copper-catalysed aromatic addition reactions.[235] Clearly, the introduction of the pyridine ring alters the reaction pathways significantly. This observation is consistent with the rationalisation that the pyridine ring is less electron-rich than the analogous phenyl ring, especially in the case of halogenated pyridines and therefore aromatic addition is disfavoured. As a result, competing reaction pathways are seen, predominantly the oxygenation pathway and when this is prevented, 1,2-hydride shift is detected as a "last resort" pathway (**Scheme 2.112**).



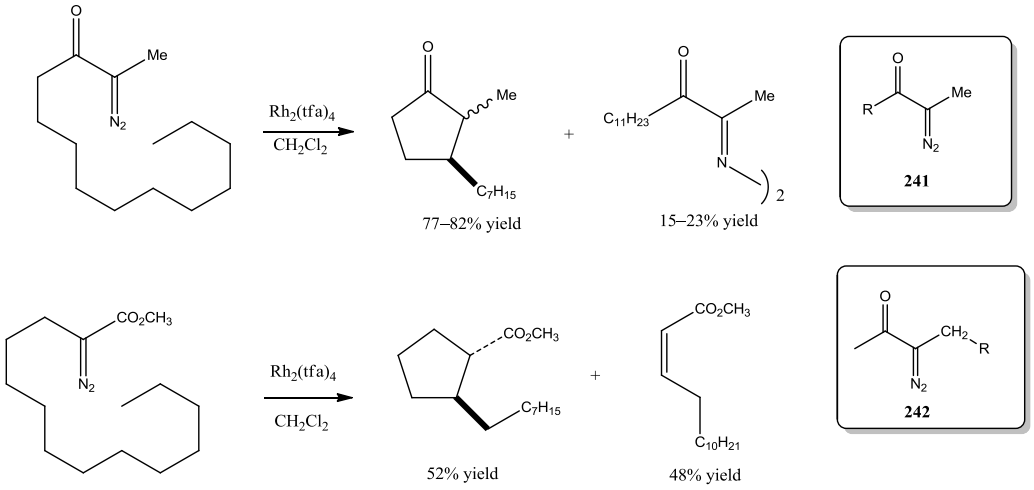
Scheme 2.112

In later work involving *O*-allyl α-diazoketone **140** (see **Section 2.4.4.2.2**), it was found that use of $Rh_2(pfb)_4$ as catalyst resulted in the formation of the corresponding terminal enone from a 1,2-hydride shift, in contrast to using $Rh_2(OAc)_4$ in the same reaction. Taber has previously demonstrated that cyclisations of a series of acyclic α-diazocarbonyl compounds in the presence of $Rh_2(pfb)_4$ preferentially formed (*Z*)-α,β-unsaturated carbonyl compounds *via* β-hydride elimination pathway in favour of a C–H insertion pathway leading to cyclopentanones (**Scheme 2.113**).[203] This can be rationalised by the presence of highly electron-withdrawing substituents on the $Rh_2(pfb)_4$ catalyst, generating a more electron-deficient and highly reactive carbenoid carbon, leading to undesired competing side reactions.



Scheme 2.113

Interestingly, earlier work by Taber and co-workers reported that reaction of α-diazo β-methyl ketones of type **241** with $Rh_2(tfa)_4$ only generated an azine dimer side product in addition to the cyclopentanone, whereas the α-diazo β-methylene ketones of type **242** provided high yields of (*Z*)-enoate using the same catalyst (**Scheme 2.114**).[236] The α-diazoketones of type **241** are similar to those investigated in our work and it appears that the formation of enones from these cyclisations is not well-precedented in comparison to using substrates **242** in the same processes.[203,236] The formation of terminal enones from alkyl and phenyl substituted α-diazoketones of type **241** has been reported previously, however, these examples of 1,2-hydide shift involved photolysis reactions[237-241] in contrast to the rhodium(II)-catalysed reactions in both Taber's[236] and our work.



Scheme 2.114

It is noteworthy that even under the strictly anaerobic conditions in our work, there was still some 2,3-diketone generated in each of the reactions, showing that completely eliminating this reaction pathway remains challenging. The ratios of enone **237** or **239** : 2,3-diketone **209** or **210** varied from 57 : 43 to 84 : 16, illustrating a certain degree of chemoselective control. In retrospect, it is likely that the trace of oxygen is introduced with the α-diazoketone which was not rigorously deoxygenated prior to addition to the rhodium(II) catalyst/solvent mixture.

While a detailed catalyst study has not been undertaken, it appears that use of $Rh_2(pfb)_4$ favours the 1,2-hydride shift, although further catalyst studies would be required to confirm this. Similarly, temperature effects appear to exert an influence on the relative amounts of the different reaction pathways. The unexpected generation of terminal enones *via* 1,2-hydride shift in transition metal-mediated reactions of **134** and **135** warrants further investigation to fully establish the critical factors involved in these processes.

2.4.3 Spiking experiments using pyridine in α-diazocarbonyl cyclisations

2.4.3.1 Background

An interesting trait of pyridine chemistry is that carbene tautomers of pyridine are possible by either a 1,2-shift or 1,4-shift of the parent substrate, as clearly described by Poveda[242] (**Figure 2.42**), while Kunz and co-workers have investigated analogous quinoline derivatives.[243] It has been observed in our work that intramolecular metallocarbenoid-mediated reactions, as seen for the phenyl analogues were unlikely, despite minimising the possibility of formation of 2,3-diketones through the use of Schlenk conditions in these reactions. It can be rationalised that the intrinsically electron-deficient pyridine ring is incompatible with reaction with the metallocarbenoid species, rendering intramolecular aromatic cycloaddition an unfavourable reaction pathway for these substrates. As there are no favoured reaction pathways available due to substrate design, *e.g.* C–H insertion, ylide formation/rearrangement or cyclopropanation, the only likely carbenoid-mediated processes appear to involve either 1,2-hydride shift, oxidation or dimerisation as "last resort" pathways. This raises the possibility that substrates where other transformations are possible, due to cogent substrate design, could prevent formation of the terminal enone and 2,3-diketone side products.

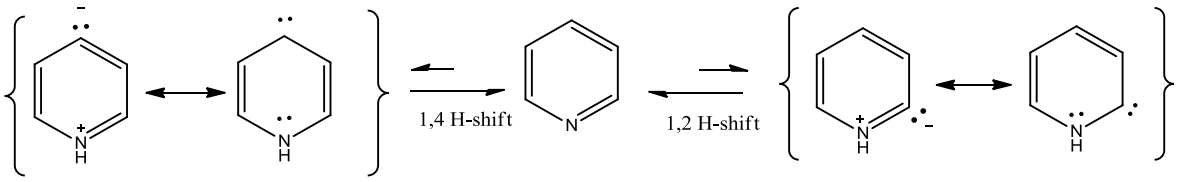


Figure 2.42: Pyridine-carbene tautomerism[242]

Interestingly, in the rhodium(II) acetate-catalysed reactions of pyridine-containing α-diazoketones in the present work, an olive green colour was observed in the reaction mixture with no colour change upon addition of the α-diazoketone to the catalyst/solvent mixture.

However, when the more electron-deficient $Rh_2(pfb)_4$ catalyst was used for this process, a pink colour was observed on addition of the α-diazoketone to the catalyst/solvent mixture. A suggested reason for this change in colour may involve coordination of the lone pair on the pyridine nitrogen to the axial positions of the Lewis acidic rhodium atoms of the catalyst. Notably, in each case the pyridine ring was halogenated; no reactions were attempted with the unsubstituted pyridine α-diazoketone **25** in this work. It is possible that increased coordination of the pyridine to the rhodium catalyst would result when the pyridine ring is not halogenated.

To explore if the pyridine ring is coordinating to the rhodium catalyst and thereby changing its reactivity, some standard α-diazocarbonyl reactions in the presence of $Rh_2(OAc)_4$ were spiked with pyridine to explore whether the catalyst activity is effected by coordination to pyridine. Work by Charette and Davies have reported that donor groups such as pyridines tend to complex to rhodium tetracarboxylates through coordination of the pyridine lone pair to the available axial positions on the rhodium (**Figure 2.43**).[244,245] This process shows selective reversible complexation to and dissociation of the pyridine from the rhodium, resulting in active and inactive forms of the catalyst, thereby permitting or preventing the reactions taking place. The two substrates investigated in this work, **243** and **245**,[167] usually lead to intermolecular cyclopropanation and intramolecular aromatic cycloaddition respectively, as illustrated in **Schemes 2.115** and **2.116**.

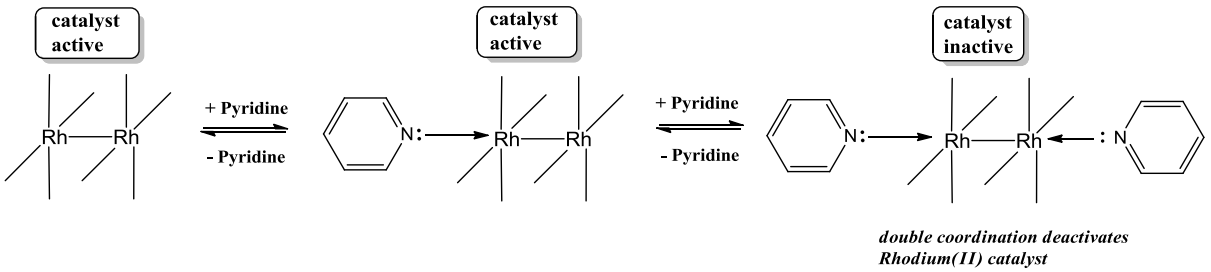
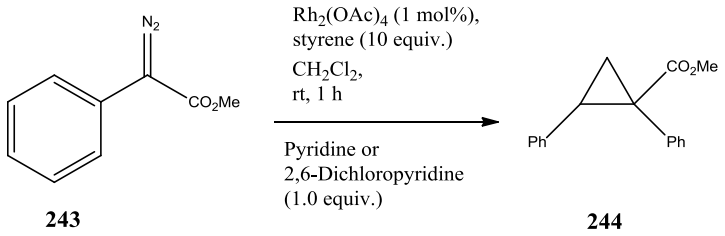


Figure 2.43: Reversible coordination of pyridine to rhodium tetracarboxylates (diagram adapted from Charette)[244]

2.4.3.2 Investigation of spiking effects using pyridine in intermolecular cyclopropanation and intramolecular aromatic addition reactions

The cyclopropanation of styrene by **243** (see **Section 3.3.1.3**) was the first reaction investigated (**Scheme 2.115**). The objective of this study was to determine if the presence of pyridine or 2,6-dichloropyridine would impact on the efficiency of the rhodium-catalysed cyclopropanation of styrene with **243**. The order of addition of pyridine relative to the other components was also explored. Thus, four experiments were undertaken;



243 **244**

Scheme 2.115

- Experiment A: The blank reaction of $Rh_2(OAc)_4$, styrene and α-diazoketone conducted by placing the rhodium catalyst (1 mol%) and styrene (10 equiv.) in dichloromethane followed by dropwise addition (15–20 min) of a solution of α-diazoketone in dichloromethane to the reaction mixture at room temperature. The reaction was complete within 1 h by TLC and infrared monitoring.

- Experiment B: The $Rh_2(OAc)_4$ catalyst and styrene were placed in dichloromethane followed by addition of the α-diazoketone. Once the addition of the α-diazoketone was complete, the reaction was stirred for 5 min and then pyridine (1.0 equiv. relative to the α-diazoketone) was added to the reaction mixture.

- Experiment C: The $Rh_2(OAc)_4$ catalyst and styrene were placed in dichloromethane followed in this case by addition of pyridine (1.0 equiv.). The reaction mixture stirred for 5 min prior to addition of the α-diazoketone.

- Experiment D: The $Rh_2(OAc)_4$ catalyst and styrene were placed in dichloromethane followed by addition 2,6-dichloropyridine (1.0 equiv. relative to the α-diazoketone) in place of pyridine. The reaction mixture was stirred for 5 min before addition of the α-diazoketone.

This series of experiments was designed to establish the impact of the addition of pyridine on the rhodium-catalysed cyclopropanation. Critically, Experiments B and C were designed to explore the difference between precoordination of the pyridine with the rhodium catalyst and addition after the introduction of the α-diazoketone. The rationale for using 2,6-dichloropyridine instead of pyridine in Experiment D was to explore the impact of the basicity of the pyridine derivative on potential coordination of the rhodium catalyst [pK_a (BH^+) pyridine 5.22,[246] pK_a (BH^+) 2,6-dichloropyridine described as 'cannot be protonated'[246] and –2.57[247]]. **Figure 2.44** below highlights the colour changes taking place during the reaction while the outcomes of these experiments were as follows;

Experiment A: Complete reaction to generate the cyclopropane **244** within 1 h and the reaction mixture remains green throughout.

Experiment B: Complete cyclopropanation observed within 1 h and the reaction mixture turns pink on addition of pyridine which indicates that the pyridine lone pair has coordinated to the catalyst, but this has only occurred after the reaction has already been catalysed.

Experiment C: No evidence of cyclopropanation within 1 h and unreacted α-diazoacetate **243** recovered. Reaction mixture was initially green, turns pink on addition of pyridine and yellow on addition of α-diazoacetate. The addition of pyridine to the catalyst prior to addition of the α-diazoacetate generates the unreactive form of the catalyst and prevents the reaction taking place.

Experiment D: Cyclopropanation is observed and the reaction mixture remains green throughout. While 2,6-dichloropyridine was added to the catalyst prior to introduction of the α-diazoacetate **243**, no coordination of the pyridine derivative to the catalyst is observed due to its negligible basicity and the reaction proceeds to generate the cyclopropane **244**.

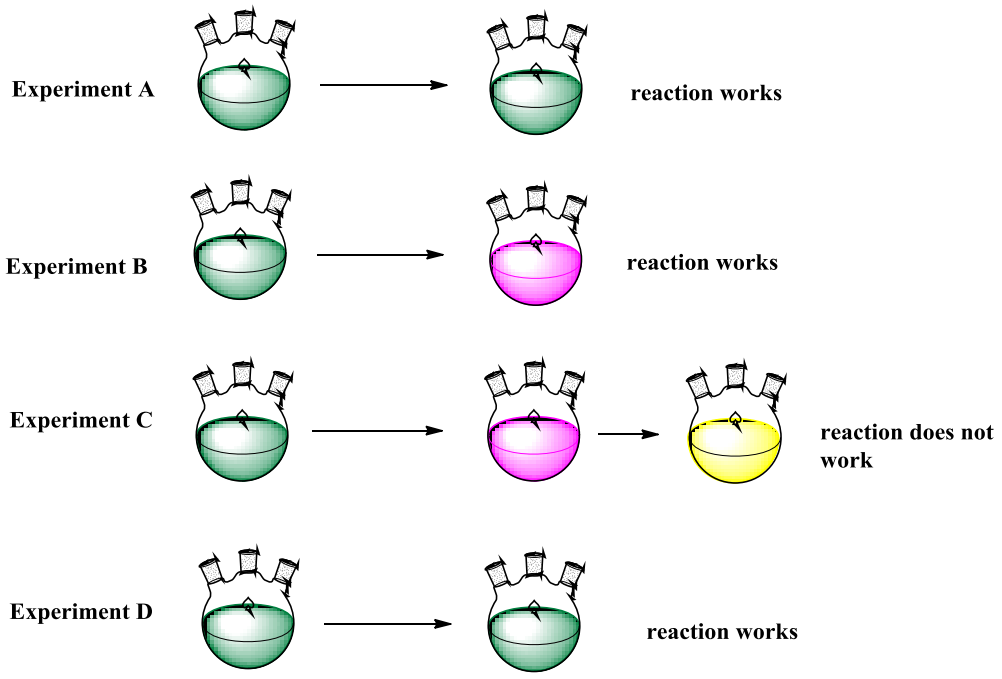


Figure 2.44: Summary of effect of pyridine substrate on the catalyst

The infrared and proton NMR spectra are summarised in **Figures 2.45** and **2.46**, showing clearly that cyclopropanation took place in Experiments A, B and D but was not observed in Experiment C. The overlaid infrared spectra below (**Figure 2.45**) illustrate that no cyclopropanation was observed for Experiment C as the peak attributed to the α-diazoacetate **243** starting material was still present at ν_{max} 2091 cm^{-1}. This is in contrast to Experiments A, B and D, where the cyclopropanation proceeds efficiently and the starting material is

transformed during the course of the reaction as evidenced by the carbonyl signal (ν_{max} 1717–1720 cm^{-1}).

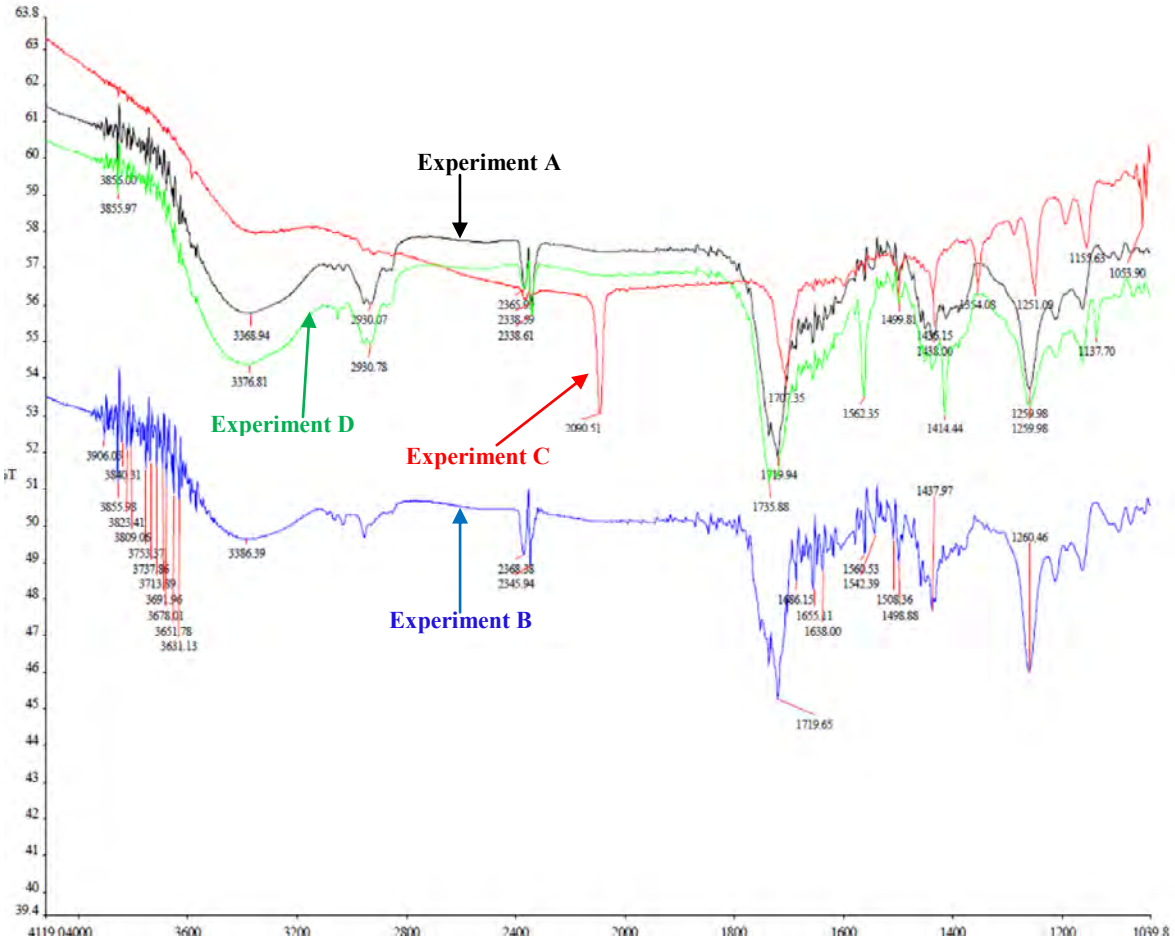


Figure 2.45: Stacked infrared spectra of attempted formation of 244 using Experiments A-D (films on NaCl)

The reaction progress, mass recovery and infrared spectral data for the attempted cyclopropanation of **243** is summarised below (**Table 2.15**).

Table 2.15 *Mass recovery and characteristic infrared stretching frequencies from attempted cyclopropanation of* ***243***

Entry	Substrate	Experiment	ν_{max}/ cm^{-1}	Reaction progress[a]	Mass recovery (%)[b]	Diazo 243	Cyclo propane 244
1	**243**	A	1720	✓	41	×	✓
2	**243**	B	1720	✓	17	×	✓
3	**243**	C	2091	×	–[c]	✓	×
4	**243**	D	1717	✓	41	×	✓

[a] Reaction progress monitored by infrared and ^{1}H NMR spectroscopy of the crude products.
[b] Mass recovery in crude-contains **244** and styrene.
[c] For Experiment C, only starting material **243** was recovered as the reaction was not catalysed.

The stacked ^{1}H NMR spectra from these reactions is shown below (**Figure 2.46**) and clearly highlight that Experiments A, B and D successfully afforded the cyclopropanation product and that the distinctive cyclopropane signals are absent in Experiment C. Signals for the cyclopropane **244** were consistent with those described in the literature,[248,249] as well as those obtained elsewhere in this work (see **Section 3.3.1.3**).

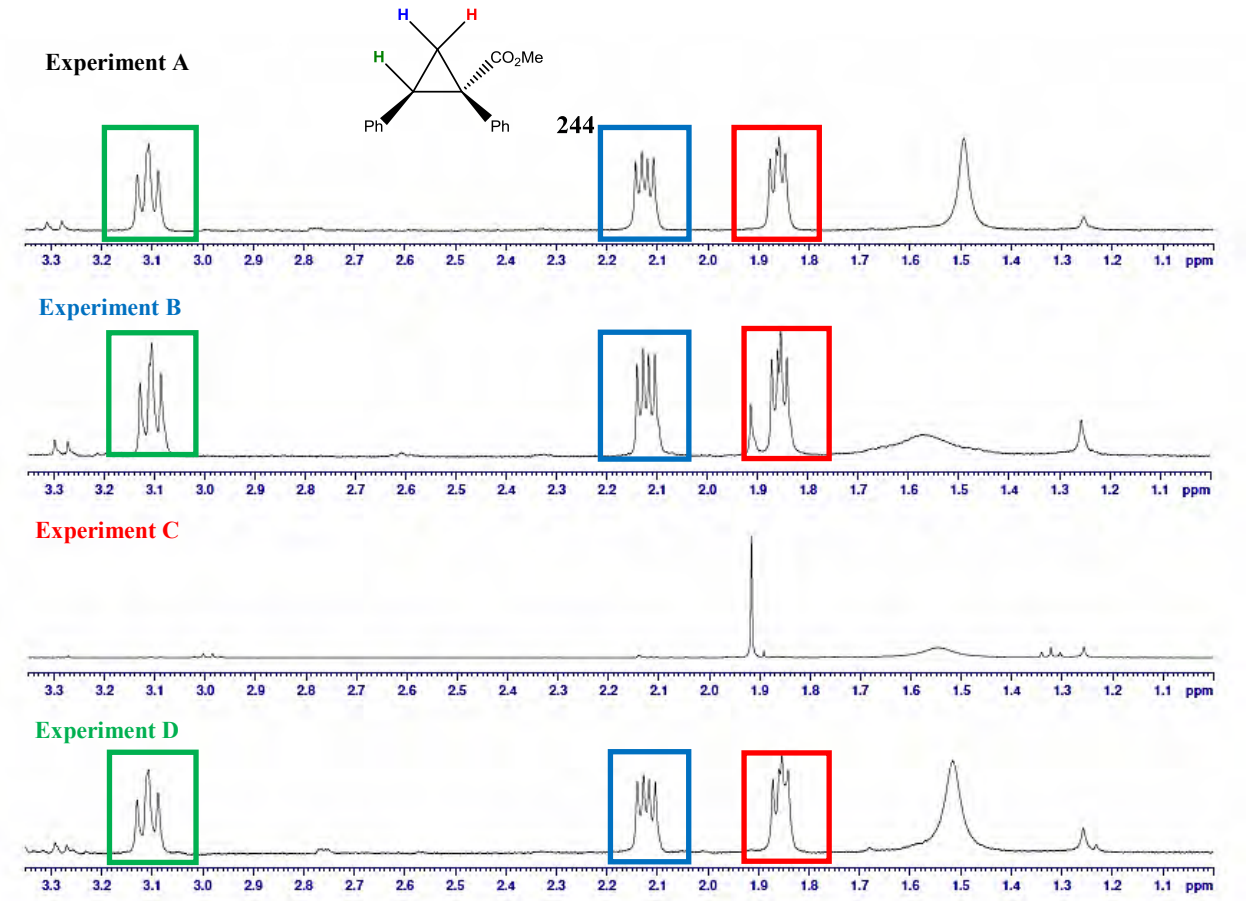
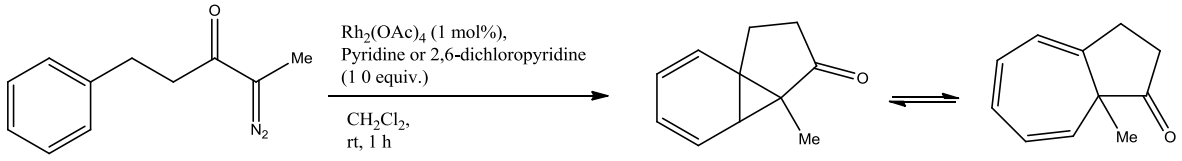


Figure 2.46: Partial ^{1}H NMR (400 MHz, $CDCl_3$) spectra of $Rh_2(OAc)_4$-catalysed cyclopropanation of styrene with 243 using Experiments A-D

These observations can be rationalised as follows: pyridine coordinates to $Rh_2(OAc)_4$ effectively poisoning the catalyst for reaction with α-diazoacetate **243** to generate the carbenoid. However, the effect is only seen when the pyridine is introduced to the catalyst prior to addition of the α-diazoacetate. In contrast, 2,6-dichloropyridine with its very low basicity does not coordinate to the rhodium and therefore has no detectable impact on the cyclopropanation of **243** with styrene.

The intramolecular aromatic addition of 4-diazo-1-phenylpentan-3-one **245**[167] was next examined (**Scheme 2.116**). In general, this is a very fast reaction which is essentially complete once the α-diazoketone is added dropwise (15–20 min) to the rhodium catalyst in dichloromethane. In this work, for consistency, each of the reactions was stirred for 1 h at room temperature in this case. The reactions were conducted following very similar protocols

to Experiments A–D above although clearly in this case without the addition of styrene. The colour changes observed during the reaction are illustrated below (**Figure 2.47**). The outcomes of these experiments followed very closely the trends seen for the intermolecular cyclopropanation and are discussed below.



245 **246**

Scheme 2.116

The outcomes of these experiments were as follows;

Experiment A: Efficient cycloheptatriene formation was observed and the reaction mixture was yellow at the end of the reaction.

Experiment B: Efficient aromatic addition to form the cycloheptatriene was observed and the reaction mixture was orange at the end of the reaction.

Experiment C: Unreacted α-diazoketone **245** was recovered with no evidence for formation of **246**. The rhodium catalyst turned pink on addition of pyridine and following addition of the α-diazoketone the reaction mixture was orange (most likely a mixture of pink and yellow).

Experiment D: Aromatic addition to form **246** is seen albeit with a more complex crude ^{1}H NMR spectrum. In this case, no colour change was evident on addition of the 2,6-dichloropyridine to the rhodium and then on addition of the α-diazoketone **245** the reaction mixture was initially orange and then faded to a pale green colour.

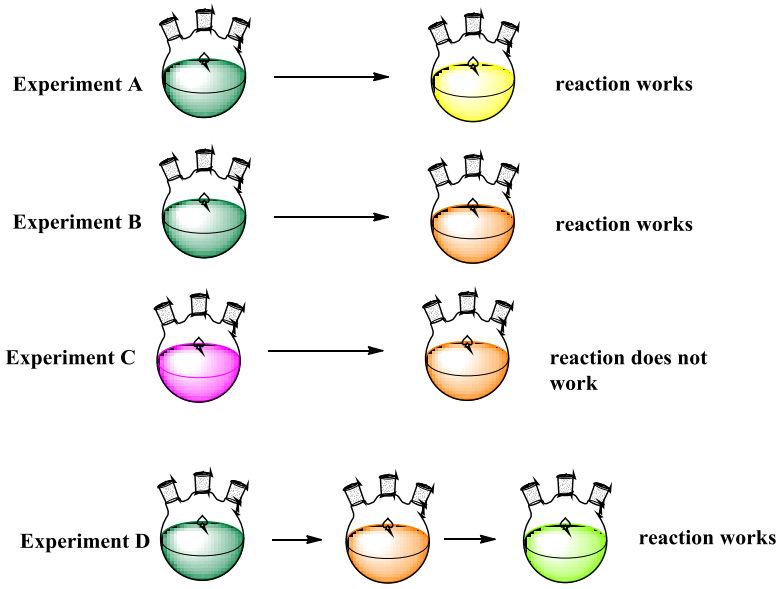


Figure 2.47: Summary of effect of pyridine substrate on the catalyst

The results obtained for substrate **245** correlate excellently with the trends observed for cyclopropanation of **243** with Experiments A, B and D providing the cycloheptatriene **246** after reaction of the α-diazoketone **245** starting material. Experiment C, in a similar way to the cyclopropanation of **243**, showed no formation of the aromatic addition product **246** due to complexation of the basic pyridine lone pair to the rhodium catalyst, generating the inactive form of the catalyst. Infrared spectroscopic analysis showed the disappearance of the diazo stretching frequency at ν_{max} 2074 cm^{-1} and emergence of a peak at ν_{max} ~1713–1715 cm^{-1} for Experiments A, B and D, while Experiment C showed the starting material **245** did not react and the characteristic diazo peak at ν_{max} 2074 cm^{-1} persisted (**Figure 2.48**). ^{1}H NMR spectroscopic data showed the characteristic cycloheptatriene peaks as a doublet at δ_H ~4.48 ppm (*J* 8.3 Hz) and a pair of multiplets at δ_H ~6.07–6.21 and ~6.26–6.35 ppm (**Figure 2.49**). Spectroscopic properties obtained for azulenone **246** were consistent with previously reported data in the Maguire group.[10]

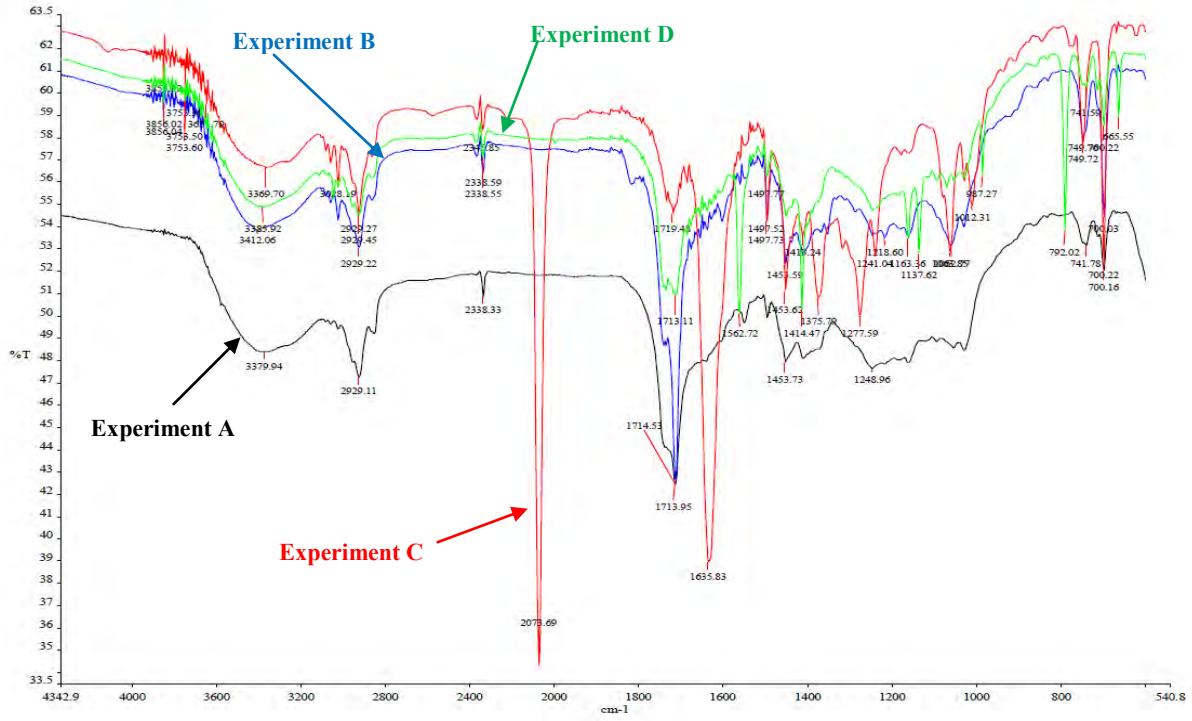


Figure 2.48: Infrared spectra of attempted formation of 246 using Experiments A-D (films on NaCl)

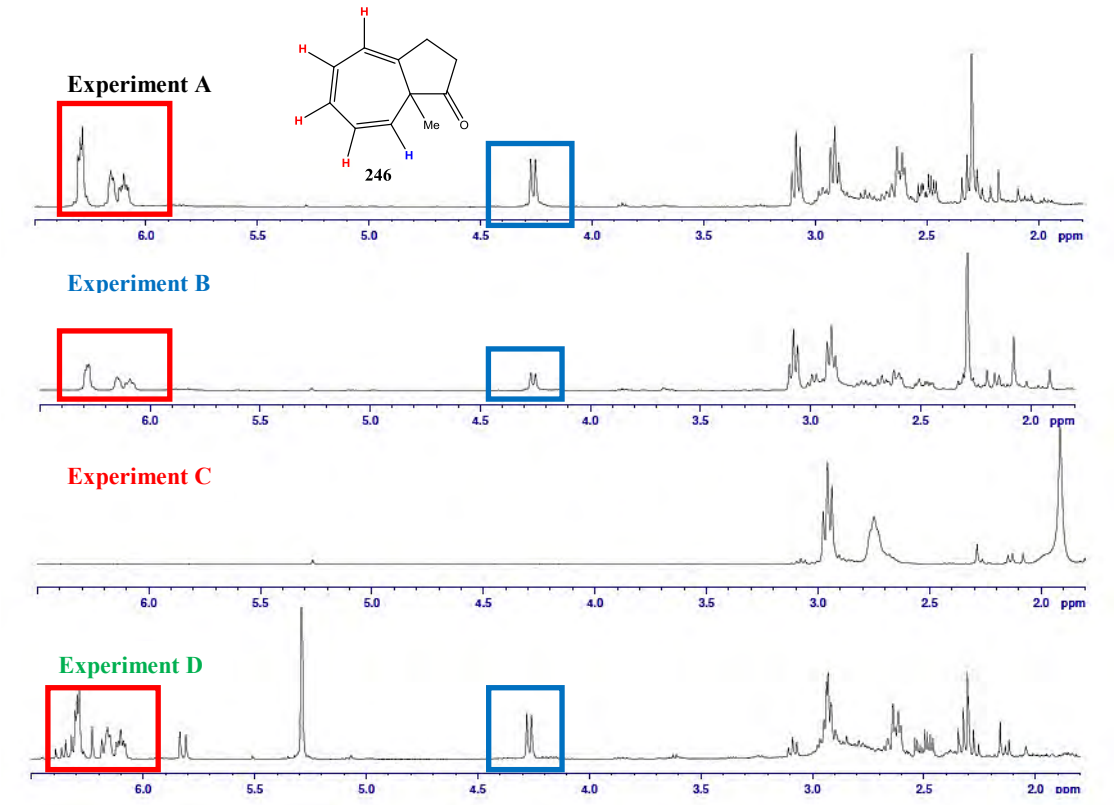


Figure 2.49: Partial ^{1}H NMR (400 MHz, $CDCl_3$) spectra of $Rh_2(OAc)_4$-catalysed aromatic addition of 245 using Experiments A-D

The reaction progress, mass recovery and infrared spectroscopic data for attempted intramolecular aromatic cycloaddition of **245** is summarised below (**Table 2.16**).

Table 2.16 *Mass recovery and characteristic infrared stretching frequencies from attempted aromatic addition of* ***245***

Entry	Substrate	Experiment	ν_{max}/ cm^{-1}	Reaction progress[a]	Mass recovery (%)[b]	Diazo 245	CHT 246
1	**245**	A	1715	✓	quant.	×	✓
2	**245**	B	1714	✓	quant.	×	✓
3	**245**	C	2074	×	–[c]	✓	×
4	**245**	D	1713	✓	quant.	×	✓

[a] Reaction progress monitored by infrared and ^{1}H NMR spectroscopy of the crude product.
[b] Mass recovery in crude-contains **246.**
[c] For Experiment C, only starting material **245** was recovered as the reaction was not catalysed.

Thus, it is observed that a sufficiently basic pyridine lone pair will coordinate and deactivate Lewis acidic rhodium(II) catalysts. However, for the samples investigated in this work, the order of the addition is vitally important as the later stage introduction of the pyridine (Experiment B) does not prevent the reaction taking place. Although the delayed addition of pyridine still results in the coordination taking place, the reaction has already been catalysed and presence of pyridine does not hinder the progress of the reaction. In the reactions of substrates **243** and **245**, it was shown that the halogenated 2,6-dichloropyridine did not

coordinate to the catalyst due its negligible basicity (Experiment D), in contrast to pyridine, and did not result in catalyst deactivation/poisoning.

Therefore, it can be concluded that in the reactions of the halogenated pyridine α-diazoketones **134-139** (see **Sections 2.4.1** and **2.4.2**), coordination of the nitrogen lone pairs to the rhodium(II) catalyst is unlikely due to the negligible basicities of the pyridine substrates, at least for the dichlorinated derivative. This is consistent with the absence of visible colour changes of the $Rh_2(OAc)_4$-catalysed reactions of the pyridine α-diazoketones **134-139**. The basicities of the various substituted pyridines used in this project are shown below, for comparative purposes (**Figure 2.50**).

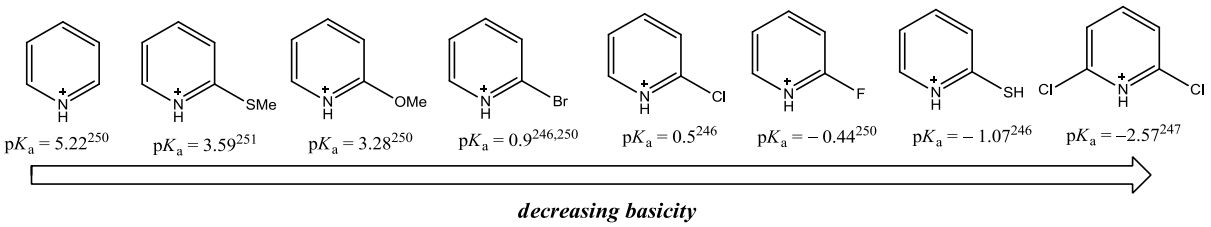


Figure 2.50: Basicities of conjugated acids of substituted pyridines[246,247,250,251]

2.4.4 Ylide formation/rearrangement and attempted C–H insertion reactions

2.4.4.1 Background

The highly electrophilic metallocarbenoids generated from α-diazocarbonyl compounds and transition metal catalysts may react with an available Lewis base to provide transient ylides (**Figure 2.51**), with these short-lived intermediates able to undergo various reaction pathways. Common reaction pathways observed include [2,3]-rearrangement of allyl and propargyl substituted ammonium, oxonium and sulfonium ylides and [1,2]-shift/Stevens rearrangement of ammonium, oxonium and sulfonium ylides, as well as competing C–H insertion reactions. In the case of carbonyl, thiocarbonyl and azomethine ylides, 1,3-dipolar cycloadditions are observed, allowing the formation of highly functionalised cycloadducts from simple components.

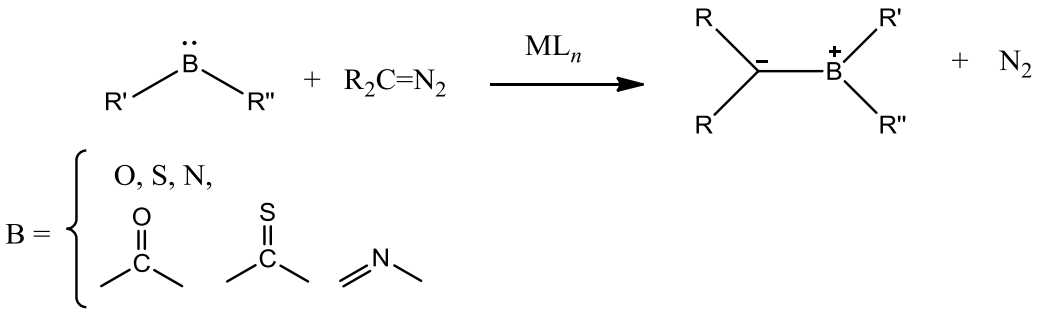
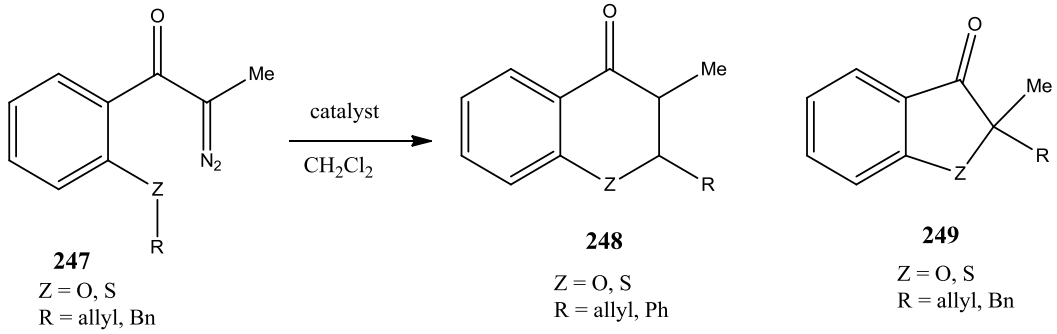


Figure 2.51: Ylide formation from α-diazocarbonyl-mediated reactions

McKervey and co-workers have extensively investigated the reaction pathways of α-diazoketones **247** possessing tethered *O*- and *S*-alkyl and aryl groups, with some interesting trends regarding chemoselectivity observed (**Scheme 2.117**).[252,253] The levels of chemoselectivity were found to be highly catalyst-dependent as different catalysts determined which of the competing pathways, C–H insertion **248** or oxonium ylide/[2,3]-sigmatropic rearrangement **249** were favoured (**Table 2.17**). This chemoselectivity demonstrated that on using rhodium(II) carboxylates with the *O*-allyl and *O*-benzyl ethers **247** (**Table 2.14**, entries 1 2 and 4), generation of the chromanone product **248** arising from C–H insertion predominated. Correspondingly, when the copper(II) acetylacetonate catalyst was employed in the same reaction, the 3-benzofuranone **249** arising from oxonium ylide/[2,3]-rearrangement was the favoured reaction pathway (**Table 2.17**, entry 1 *vs.* 3).

In the same study, McKervey further probed the reactions of allyl substituted compounds with the cyclisation of *S*-allyl α-diazoketone **247** (**Table 2.17**, entry 5).[253] Unlike the oxygen-substituted allylic counterpart (**Table 2.17**, entry 1), which favoured formation of C–H insertion product **248** in the presence of rhodium(II) acetate, cyclisation of the *S*-allyl α-diazoketone in the presence of rhodium(II) acetate exclusively provided the sulfonium ylide/[2,3]-rearrangement product **249** (**Table 2.17**, entry 1 *vs*. 5).



247
Z = O, S
R = allyl, Bn

248
Z = O, S
R = allyl, Ph

249
Z = O, S
R = allyl, Bn

Scheme 2.117

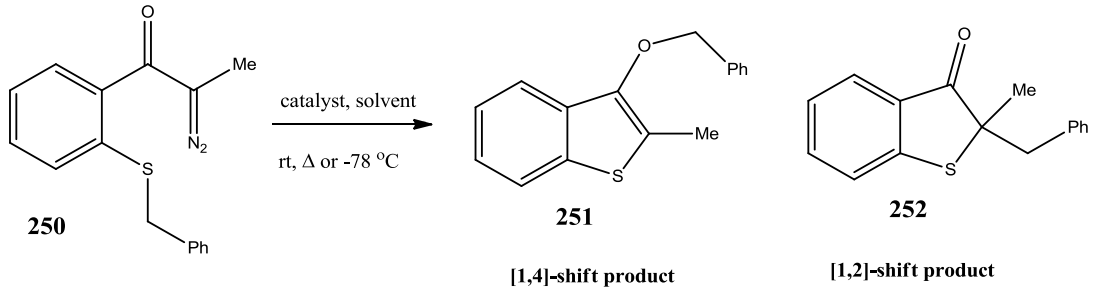
Table 2.17 *Formation of **246** and **247** using rhodium and copper catalysts*[253]

Entry	Z	R	Catalyst	248[a]	249[a]
1	O	allyl	$Rh_2(OAc)_4$	97	3
2	O	allyl	Rh_2(*S*-BSP)$_4$	97	3
3	O	allyl	$Cu(acac)_2$	0	100
4	O	Bn	$Rh_2(OAc)_4$	100	0
5	S	allyl	$Rh_2(OAc)_4$	0	100

[a] Isolated yield after column chromatography. Crude ratios were not reported.

Mountjoy has extended the work on sulfonium ylides through investigating the reaction pathways of *S*-benzyl α-diazoketone **250** (**Scheme 2.118**).[25] In that work, an unexpected [1,4]-shift product **251**, as well as anticipated [1,2]-shift product **252** were formed. The product distribution was shown to be dependent on the temperature, solvent and to a minor extent, the electronic nature of the rhodium(II) catalyst (**Table 2.18**). In addition, Twomey in our research group also investigated reactions of α-diazoketone **250** through a series of

crossover experiments to establish the inter- or intramolecular nature of the radical recombination to generate [1,4]-shift product **251**.[52]



Scheme 2.118

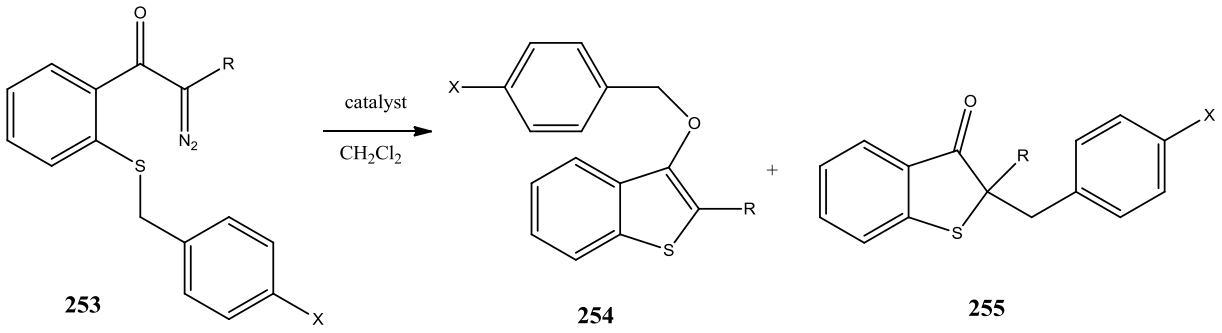
Table 2.18 *Generation of **251** and **252** using rhodium catalysts*[25]

Entry	Catalyst	Solvent	Temperature	251[a]	:	252[a]
1	$Rh_2(OAc)_4$	CH_2Cl_2	rt	3.06		1
2	$Rh_2(OAc)_4$	CH_2Cl_2	reflux	1.67		1
3	$Rh_2(OAc)_4$	CH_2Cl_2	–78 °C to rt	8.21		1
4	$Rh_2(pfb)_4$	CH_2Cl_2	rt	2.62		1
5	$Rh_2(mand)_4$	CH_2Cl_2	rt	3.86		1
6	$Rh_2(OAc)_4$	Toluene	reflux	0.89		1

[a] These reactions were conducted on 20 mg scale with ratios determined by crude ^{1}H NMR; no purification was attempted.[25]

Further work in our group by Mountjoy showed that the introduction of electron-withdrawing groups (*p*-NO_2) and electron-donating groups (*p*-OMe) on the benzyl substituent of the α-diazoketone **253** were also found to exert an influence in determining which reaction pathway was favoured (**Scheme 2.119**).[25] Reaction of *para*-methoxy compound **253** (**Table 2.19**, entry 1) in the presence of $Rh_2(OAc)_4$ provided the [1,4]-rearrangement product **254** exclusively. An interesting corollary was observed for the *para*-nitro substituted compound **253** (**Table 2.19**, entry 2), resulting in [1,2]-shift product **255** emerging as the dominant reaction pathway.

Finally, Murphy examined the effect of replacing the methyl group adjacent to the diazo moiety with a strongly electron-withdrawing methylsulfonyl group, SO_2Me.[254] Findings from Murphy's work showed that for the simple non-substituted α-diazo-β-ketosulfone **253** (**Table 2.19**, entries 3 and 4), the reaction outcome was highly dependent on the catalyst, with the copper catalysts providing more efficient reactions and higher isolated yields of rearrangement products **254** and **255**. In both cases, formation of the [1,2]-rearrangement product **255** was the dominant reaction pathway.



Scheme 2.119

Table 2.19 *Formation of* ***254*** *and* ***255*** *from cyclisations of α-diazoketones*[25] *and α-diazo-β-ketosulfones*[254]

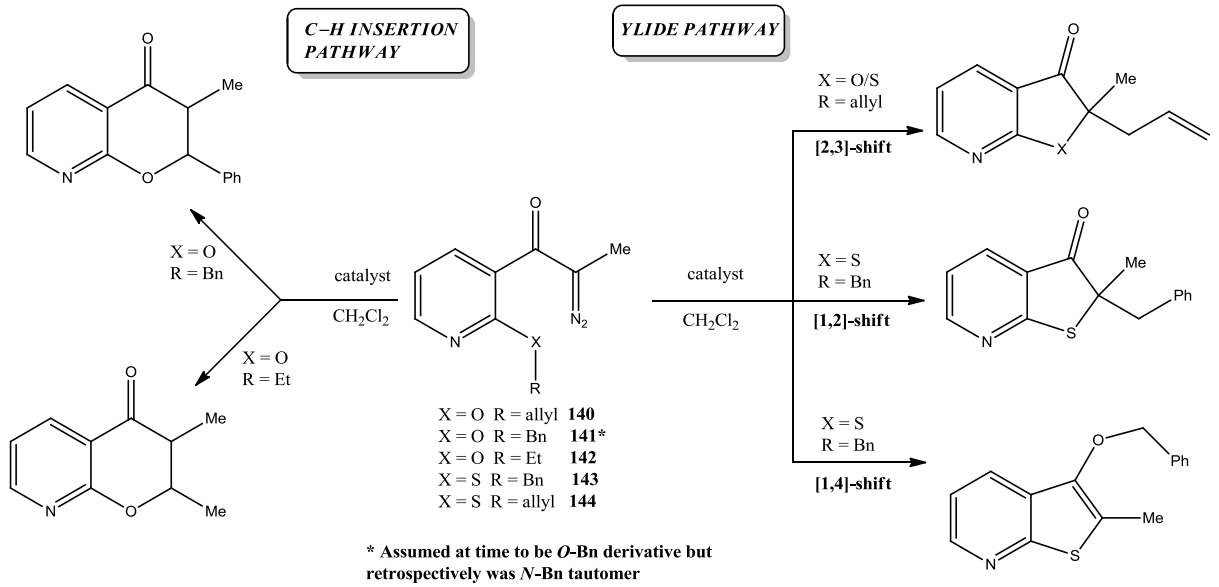
Entry	R	X	Catalyst	Yield (%)	
				254[a]	**255**[a]
1	Me	NO_2	$Rh_2(OAc)_4$	15	24
2	Me	OMe	$Rh_2(OAc)_4$	71	0[b]
3	SO_2Me	H	$Rh_2(OAc)_4$	7	67
4	SO_2Me	H	$Cu(acac)_2$	41	54

[a] Purified yields. Crude ratios not reported.
[b] Benzothiophenone **255** not detected

2.4.4.2 Transition metal-catalysed transformations of α-diazoketones for ylide formation/rearrangement and C–H insertion reactions

Having established that rhodium-catalysed transformations of α-diazoketones bearing pyridyl substituents is possible, our study next focused on pyridyl α-diazoketones **140-144** designed to enable exploration of ylide formation and subsequent reaction pathways. Furthermore, investigation of the influence of catalyst was undertaken (**Scheme 2.120**). While earlier rhodium-catalysed reactions were conducted at room temperature (**Sections 2.4.1** and **2.4.2**), in this section the rhodium-catalysed reactions were conducted under reflux and were not attempted at room temperature. The substrates **140–144** employed for these reactions enable a direct comparison to the phenyl systems investigated by McKervey[253] and Mountjoy,[25] with differences in the reaction pathways between the analogous substrates of particular interest.

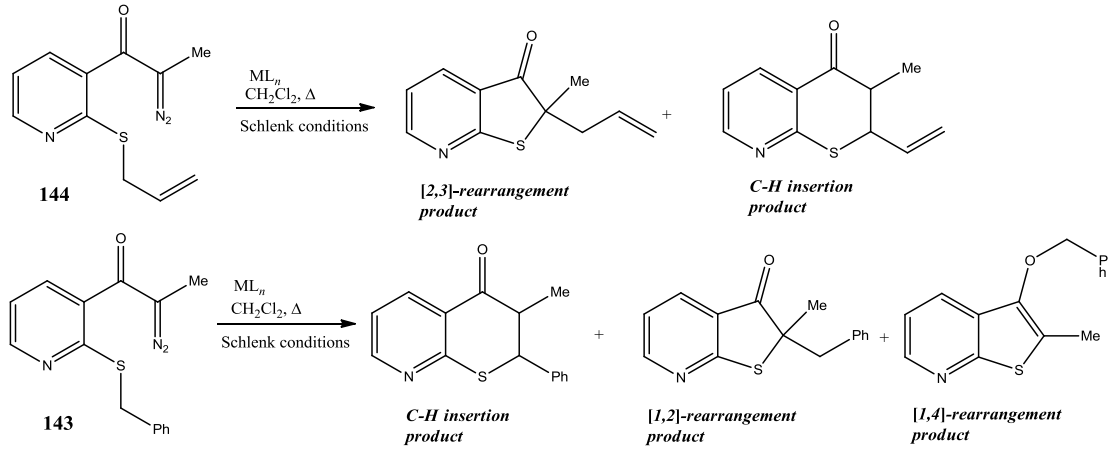
As was the case for some of the reactions undertaken by McKervey,[253] there is potential to extend the transition metal-mediated processes for enantioselective ylide formation/rearrangement and C–H insertion reactions. Successful results for these transformations will serve as an excellent starting point in any future asymmetric catalysis attempted for these compounds.



Scheme 2.120: Possible reaction pathways of oxygen- and sulfur-containing pyridine α-diazoketones 140-144

2.4.4.2.1 Transition metal-catalysed reactions of sulfur-containing α-diazoketones

The two substrates investigated in this work were the *S*-allyl α-diazoketone **144** and *S*-benzyl α-diazoketone **143**. The possible reaction outcomes were thought to involve sulfonium ylide/rearrangement or C–H insertion (**Scheme 2.121**) and the catalyst-dependent nature of these transformations was explored. All the products from the rearrangements in this work were novel and were characterised as far as possible.

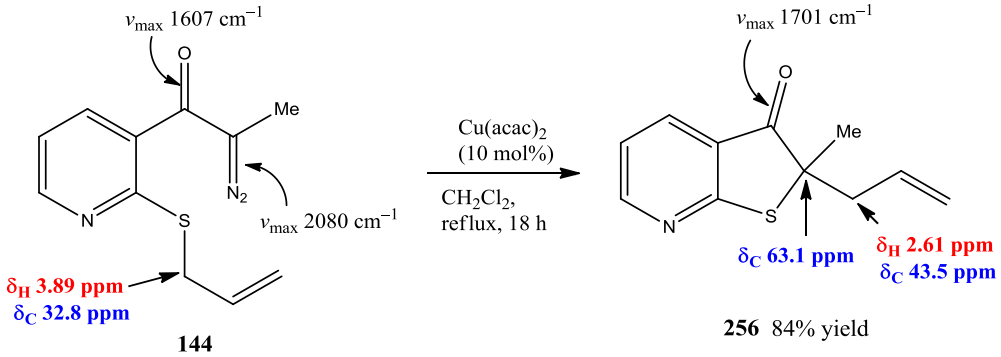


Scheme 2.121

Each of the reactions in this section were conducted using dropwise addition of a solution of α-diazoketone to the catalyst in dichloromethane which had been pre-refluxed for 3 h and reactions were carried out under Schlenk conditions to exclude any traces of oxygen, preventing possible formation of 2,3-diketone side products. In each case, the reaction progress was monitored by infrared spectroscopy and TLC. In general, crude ^{1}H NMR spectroscopic analysis was not carried out with the exception of reactions of *S*-benzyl α-

diazoketone **143**. There was no sign of a colour change on addition of the α-diazoketone to the reactions apart from cyclisations in the presence of $Rh_2(pfb)_4$ catalyst (see below **Table 2.21**, entry 4), which is consistent with results observed elsewhere in this work. As a general trend for these cyclisations, the reactions went to completion in shorter times for the rhodium than the copper catalysts.

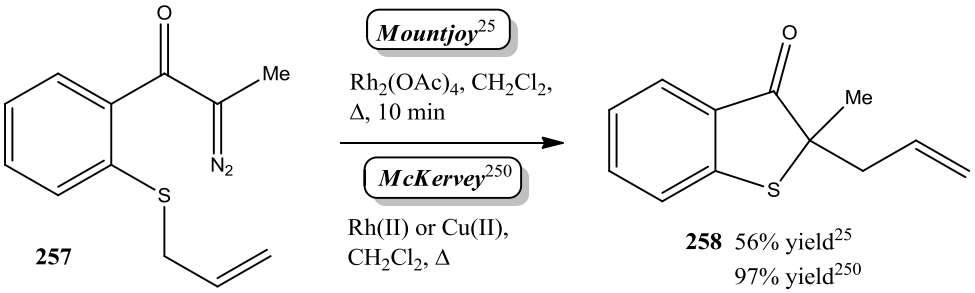
The first compound explored in this study was *S*-allyl α-diazoketone **144**. Reaction conditions involved addition of a solution of **144** in doubly distilled dichloromethane to a refluxing solution of copper(II) acetylacetonate in doubly distilled dichloromethane (**Scheme 2.122**). The reaction mixture was heated under reflux for 18 h, at which point monitoring by infrared spectroscopy and TLC analysis indicated complete disappearance of the α-diazoketone. Following chromatography, the [2,3]-rearrangement product **256** was isolated exclusively in 84% yield from the initially formed sulfonium ylide, with no indication of any C–H insertion product.



Scheme 2.122: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125.8, $CDCl_3$) values for 144 and 256

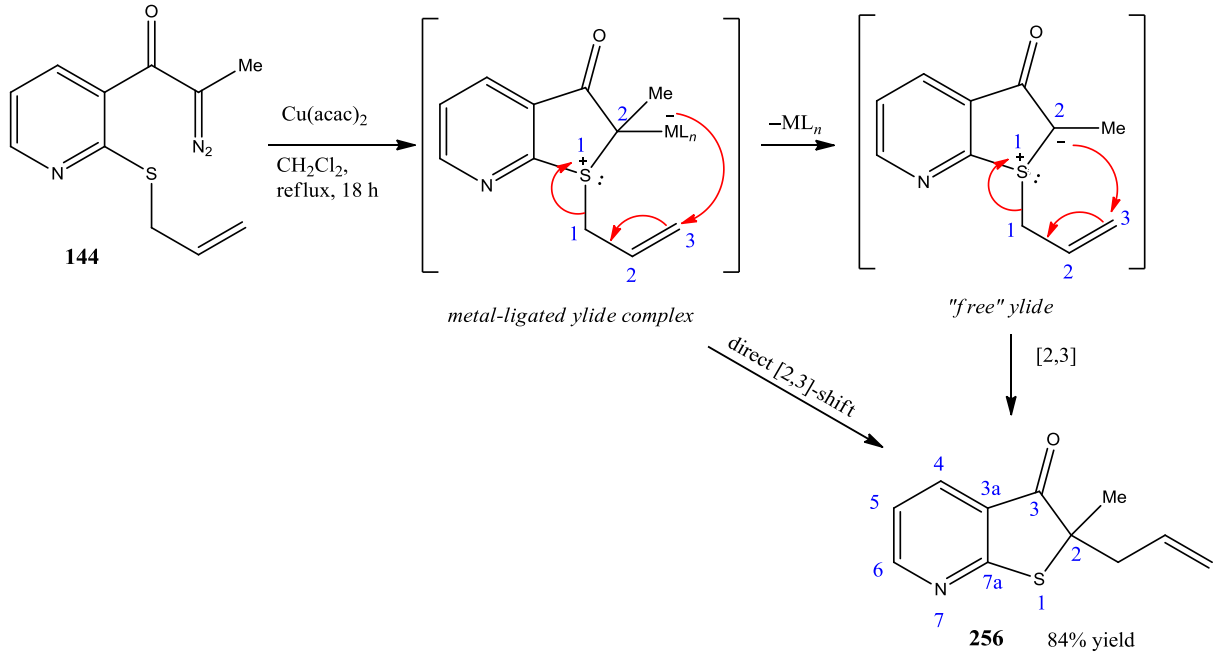
Structural identity of the novel rearrangement product **256** was confirmed by ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, as well as mass spectrometry. Characteristic signals in ^{1}H NMR spectrum of **256** include the appearance of a doublet at δ_H 2.61 ppm accounting for the methylene group previously attached to the sulfur atom, which is now attached to a carbon atom. The signal for this carbon, C(2)$\underline{C}H_2CHCH_2$, is located at δ_C 43.5 ppm in the ^{13}C NMR spectrum of **256**. These values have dramatically shifted from the parent α-diazocarbonyl compound **144**, as the corresponding values were observed as a doublet of triplets at δ_H 3.89 ppm and a signal at δ_C 32.8 ppm respectively (**Scheme 2.122**). Infrared spectroscopic analysis clearly indicated reaction of the diazo group and identification of the carbonyl band ascribed to the bicyclic product **256** at ν_{max} 1701 cm^{-1} (**Scheme 2.122**). Proton and ^{13}C NMR analysis were in excellent agreement with spectroscopic data for the analogous phenyl rearrangement product **258** previously prepared by both McKervey[253] and Mountjoy (**Scheme 2.123**),[25] while the carbonyl stetch in the infrared analysis deviated slightly from the value of ν_{max} 1695 cm^{-1} disclosed by Mountjoy.[25] As a limited amount of α-diazoketone **144** was synthesised, the cyclisation was only carried out in the presence of copper(II) acetylacetonate.

Comparison of the outcome of the copper-catalysed reaction of **144** to give exclusively the [2,3]-rearrangement product **256** with Mountjoy's[25] report of the corresponding phenyl α-diazoketone **257** to provide similarly **258**, the product of [2,3]-rearrangement is interesting. McKervey also reported exclusive sulfonium ylide formation/[2,3]-rearrangement in the phenyl system although is not clear which catalyst was used in that study.[253] Thus, replacement of the phenyl ring with the pyridyl ring appears to make no difference on the reaction pathways.



Scheme 2.123

The possible mechanistic interpretations involve dissociation of the metal from the fleeting sulfonium ylide to provide a "free" ylide prior to rearrangement or concurrent displacement of the metal from the metal-ligated complex and rearrangement to furnish **256** (**Scheme 2.124**). Rearrangement *via* the metal-ligated complex pathway would enable retention of stereochemical information, with asymmetric induction engendered from the chiral ligands on the transition metal catalyst if a chiral catalyst is employed.



Scheme 2.124: Mechanism of sulfonium ylide formation/[2,3]-sigmatropic rearrangement from metal-ligated ylide complex or "free" ylide

This [2,3]-rearrangement involves scission of a σ-bond followed by formation of a new carbon–carbon bond between two neighbouring π-bonds and generation of a new stereogenic centre in the process (**Figure 2.52**).[255]

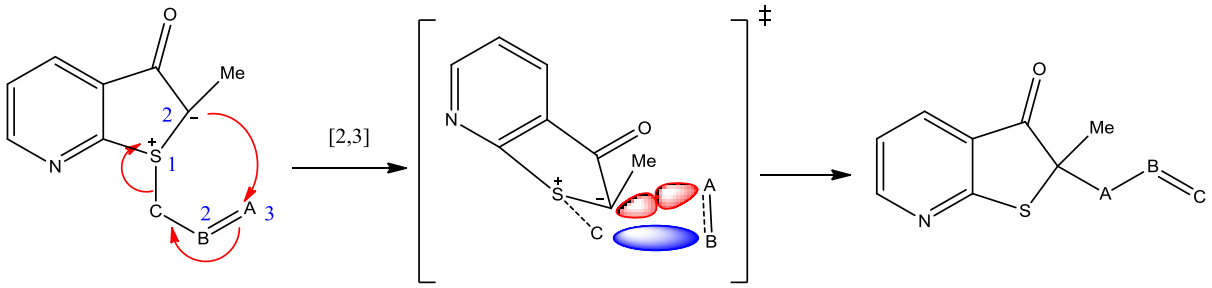
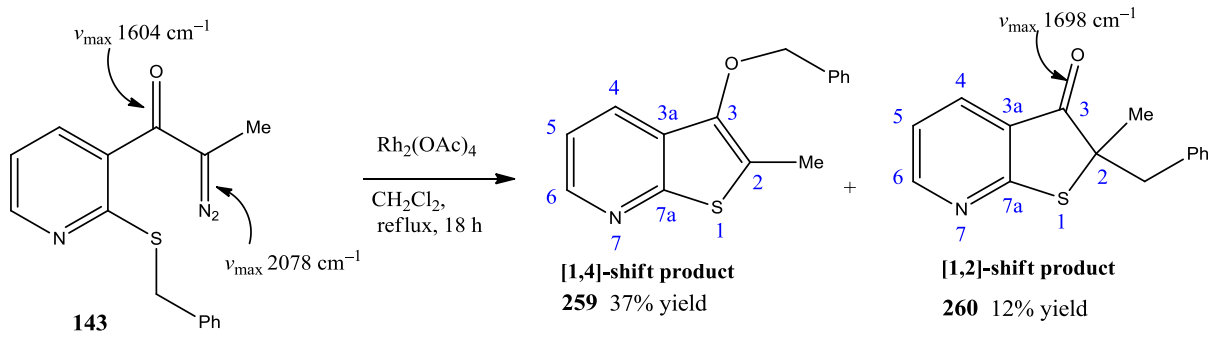


Figure 2.52: Illustration of bond cleavage and formation in [2,3]-sigmatropic rearrangement of 256 (adapted from Sweeney)[255]

The conditions employed in the cyclisation of **144** were repeated for all subsequent attempted ylide formation/rearrangement and C–H insertion reactions. The α-diazoketone was added dropwise over ~1 h to a refluxing solvent/catalyst mixture and the reaction progress was monitored after 18 h at reflux by infrared spectroscopy and TLC analysis. As a general trend for these cyclisations observed, the reactions went to completion in shorter times for the rhodium catalysts than the copper catalysts.

Transition metal-catalysed reactions involving *S*-benzyl diazoketone **143** were next investigated (**Scheme 2.125**). This transformation was initially carried out using rhodium(II) acetate (**Table 2.20**, entry 3) and the crude ^{1}H NMR spectrum indicated the possible formation of products arising from both [1,2]- and [1,4]-benzyl migration of the sufonium ylide intermediate. Purification by flash chromatography resulted in isolation of both the [1,4]-rearrangement product **259** and [1,2]-shift product **260** as a colourless or pale yellow oil, which correlates very well with Mountjoy's work on the analogous phenyl derivative where the C–H insertion product was not detected and both benzyl-rearrangement products were successfully prepared.[25] Rearrangement product **259** was isolated as the less polar compound and compound **260** was observed as the more polar component, while the [1,4]-shift product **259** was observed as the major product isolated from the reaction, in agreement with Mountjoy's studies identifying the [1,4]-shift as the favoured rearrangement pathway. Further investigations by Mountjoy focused on the influence of different solvents, temperatures and reaction times on the distribution of the [1,4]- and [1,2]-shift products.[25] In that work, the ratio of both components was established by integration of the benzylic signals, $OC\underline{H_2}C_6H_5$, in the crude ^{1}H NMR spectrum and no purification was attempted. In the current investigation, the ratio of **259** : **260** was also established by integration of the signals in the crude ^{1}H NMR spectrum (**Table 2.20**).



Scheme 2.125

The signals for both [1,2]- and [1,4]-shift products, both novel compounds, are very distinctive in the ^{1}H, ^{13}C NMR and infrared spectra (**Figure 2.53**). These compounds were also characterised by nominal and high resolution mass spectrometry. For the [1,4]-shift product **259**, ^{1}H NMR spectroscopic analysis identified the signal for the methyl group as a singlet at δ_H 2.34 ppm and the singlet for the benzylic protons, O$\underline{CH_2}C_6H_5$, is seen at δ_H 5.05 ppm. This signal is located further downfield than the corresponding signal for the [1,2]-shift product **260**, due to the deshielding effect of the adjacent oxygen atom. The major signals of note in the ^{13}C NMR spectrum include a substantial shift of the benzylic signals from δ_C 64.4 ppm for α-diazoketone **143** to δ_C 75.9 ppm for **259**, as well as the identification of the quaternary carbon at δ_C 125.8 or 127.9 ppm for **259**, in contrast to the value of δ_C 64.4 ppm for **260** (**Figure 2.53**). Infrared spectroscopy of **259** displayed an absence of a carbonyl signal, indicating that the [1,4]-rearrangement has taken place. The stacked ^{1}H NMR spectra of benzyl migration products **259** and **260** are shown below (**Figure 2.54**).

In the ^{1}H NMR spectrum of [1,2]-rearrangement product **260**, the benzylic methylene group, C$\underline{CH_2}C_6H_5$, is observed as an AB quartet (ABq) at δ_H 3.13 and 3.18 ppm. Other characteristic signals in the ^{1}H NMR spectrum of **260** include identification of the methyl group as a singlet at δ_H 1.62 ppm. In the ^{13}C NMR spectrum, the corresponding value for the benzylic carbon, C$\underline{C}H_2C_6H_5$, is seen at δ_C 45.0 ppm *cf.* δ_C 65.6 ppm in the starting material **143**, while the signal for the quaternary carbon is observed at δ_C 64.4 ppm (**Figure 2.53**). Infrared spectroscopic analysis of **260** highlighted a band corresponding to the carbonyl stretch at ν_{max} 1698 cm^{-1}.

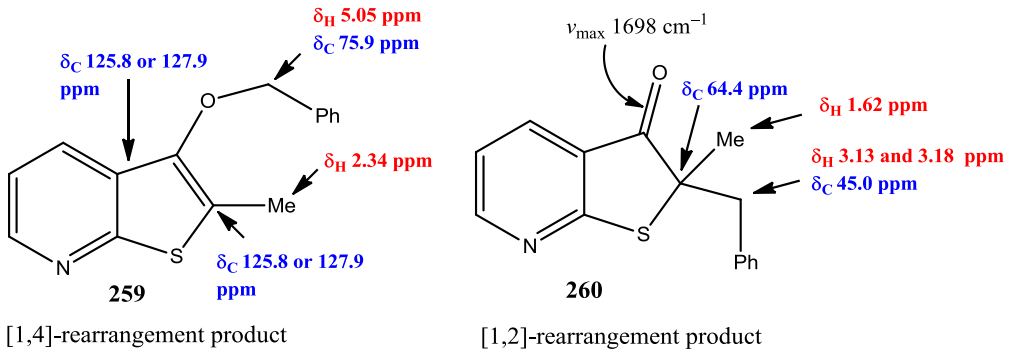


Figure 2.53: ^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (125.8, $CDCl_3$) and infrared data

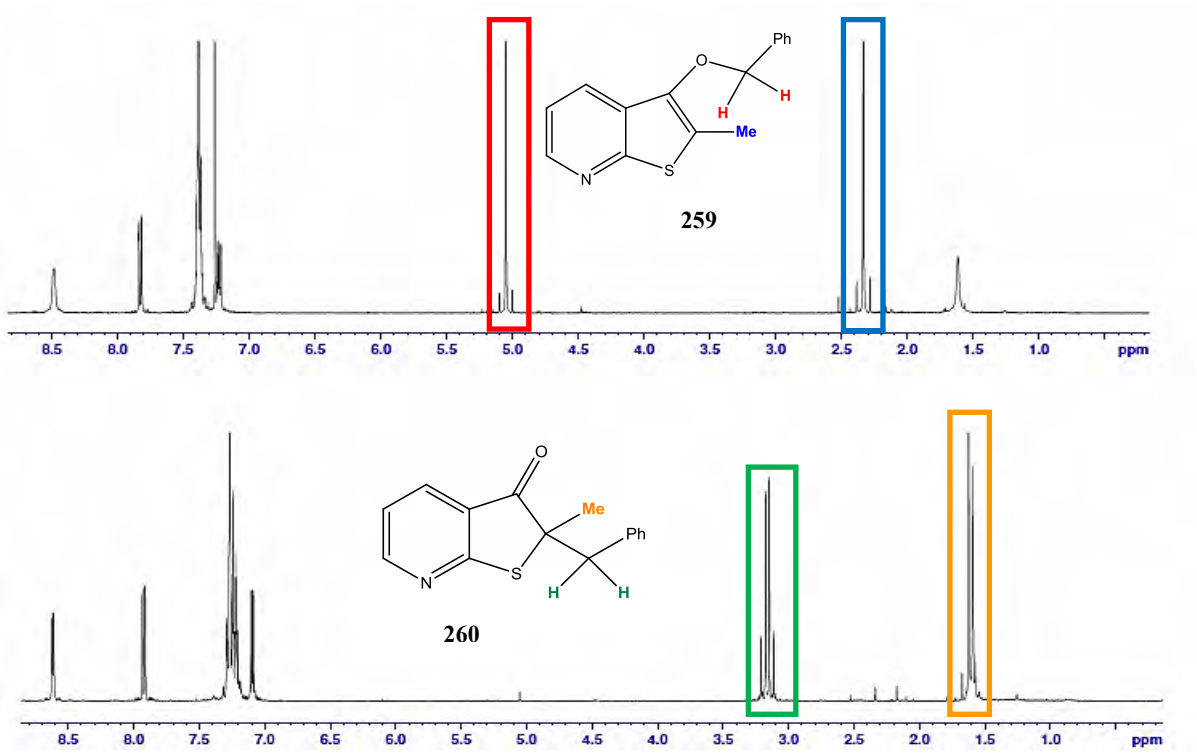
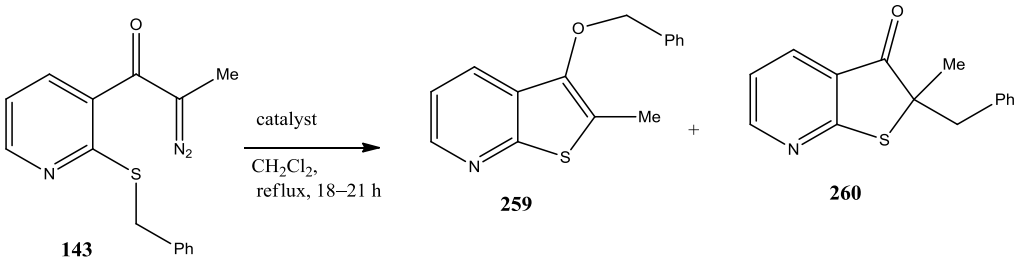


Figure 2.54: ^{1}H NMR (400 MHz, $CDCl_3$) spectra of [1,4]- and [1,2]-rearrangement products 259 and 260 (signal for [1,2]-shift product slightly overlaps with signal for residual water at δ_H ~1.6 ppm)

Following initial ylide formation/rearrangement of **143** in the presence of rhodium(II) acetate, cyclisation of **143** employing other catalysts was undertaken with copper(II) acetylacetonate, copper(II) hexafluoroacetylacetonate and rhodium(II) perfluorobutyrate next examined. These catalysts also afforded both benzyl migration products **259** and **260** with the [1,4]-shift product **259** emerging as the dominant reaction pathway in all cases. The isolated yields were reasonably consistent with the exception of copper(II) acetylacetonate (**Table 2.20**, entry 2), which resulted in a slightly lower yield. This was also the slowest reaction and was not complete after 18 h as determined by infrared and TLC monitoring, requiring an additional 3 h for the reaction to go to completion. Interestingly, the crude ^{1}H NMR spectra for reactions conducted using the rhodium catalysts were cleaner than those from the reactions using the copper catalysts. In all reactions, the crude ratio and comparative isolated yield demonstrated that the formation of the [1,4]-rearrangement product **259** was strongly favoured. These results are summarised below (**Table 2.20**).

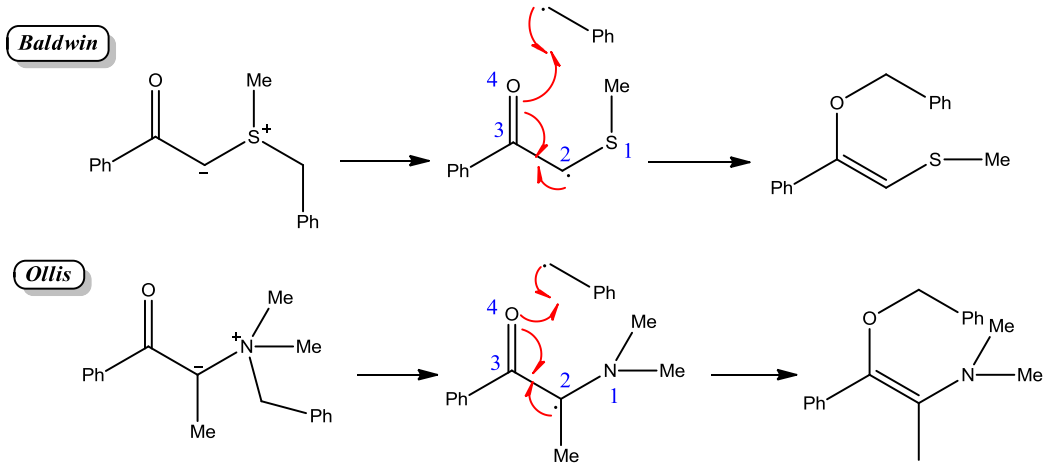
Table 2.20 *Transition metal-catalysed sulfonium ylide/rearrangement of 1-[2-(benzylthio)pyridin-3-yl]-2-diazopropan-1-one* **143**[a]



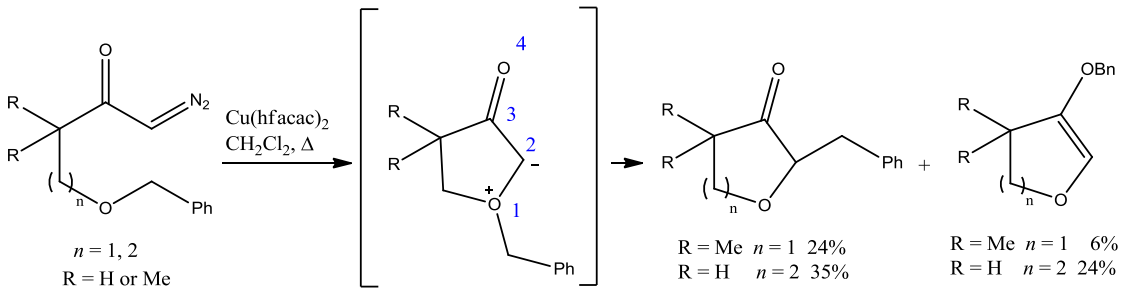
Entry	Catalyst	Time (h)	259: 260[b]	Yield 259 (%)[c]	Yield 260 (%)[c]
1	$Cu(hfacac)_2$	18	76 : 24	33	13
2	$Cu(acac)_2$	21[d]	77 : 23	19	5
3	$Rh_2(OAc)_4$	18	75 : 25	37	12
4	$Rh_2(pfb)_4$	18	75 : 25	38	8

[a] Reactions conducted using the general procedure for rhodium(II)- and copper(II)-catalysed C–H insertion and/or ylide formation/rearrangement reactions.
[b] Ratio of **259** : **260** established by integration of benzylic $C\underline{H}_2$ signals in crude ^{1}H NMR spectrum
[c] Isolated yield after column chromatography.
[d] Reaction not complete after 18 h as determined from monitoring by infrared spectroscopy and TLC.

One of the key points arising from Mountjoy's[25] and Twomey's[52] work was the origin of the [1,4]-rearrangement product and the possibility that the rearrangement occurs from the ylide, with subsequent radical recombination. Work by Baldwin in 1970[256] and Ollis in 1983[257] were the earliest examples of definitive [1,4]-rearrangements from sulfonium and ammonium ylides respectively. Base-promoted deprotonation of ammonium and sulfonium salts resulted in the generation of ammonium and sulfonium ylides, which subsequently rearranged *via* radical dissociation-recombination process (**Scheme 2.126**).[256,257] West has described that a competitive [1,2]- and [1,4]-benzyl migration can occur in oxonium ylides derived from acyclic α-diazocarbonyl compounds in the presence of $Cu(hfacac)_2$ and it is postulated this process may occur *via* radical pair intermediates (**Scheme 2.127**).[258]

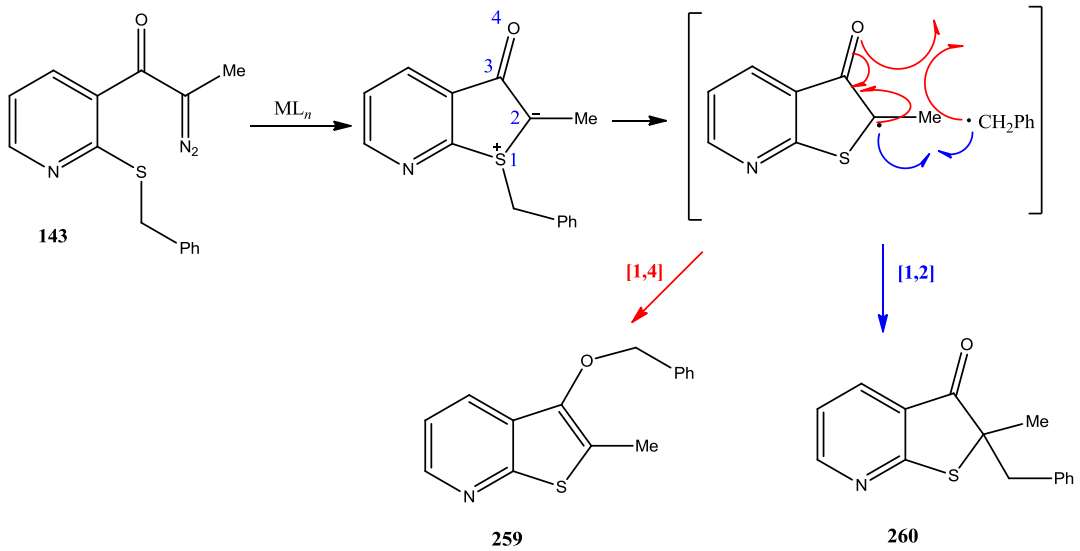


Scheme 2.126: [1,4]-rearrangements by both Baldwin[256] and Ollis[257]



Scheme 2.127: [1,2]- and [1,4]-rearrangements observed by West[258]

In the case of *S*-benzyl α-diazoketone **143** in this work, formation of the [1,4]-shift product **259** can be envisioned to stem from radical recombination at the oxygen in preference to the α-carbon (**Scheme 2.128**). It is also possible that metal-assisted homolysis/recombination could be involved in the generation of the [1,2]- and [1,4]-rearrangement products.

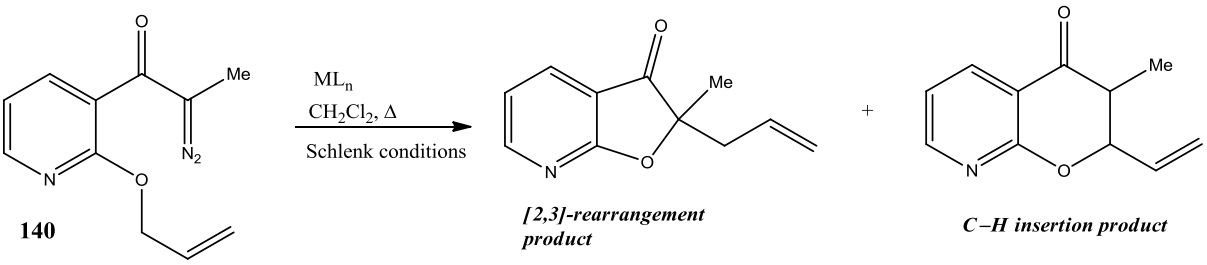


Scheme 2.128: Formation of both [1,2]- and [1,4]-shift products from cyclisation of 143

The formation of a [1,4]-shift product in 'onium' ylide/rearrangement transformations is generally reported as a side product in low to negligible yields, as opposed to the dominant reaction pathway encountered in this work and in earlier studies by Mountjoy.[25] The driving force in the formation of the [1,4]-shift product can perhaps be rationalised by the generation of the fully aromatised heterocycles in both this and Mountjoy's work. For tandem ylide formation/rearrangement processes involving pyridine derivatives, there is certainly scope to expand substituted benzyl derivatives (*e.g.* *p*-OMe, *p*-NO_2) to explore electronic effects on the distribution of the [1,2]- and [1,4]-shift products, rationalised by the tuning of the reactivity and stability of the benzylic radical due to the electronic nature of the substituents. The changing of parameters such as solvent and temperature can also be further probed in future work on these compounds.

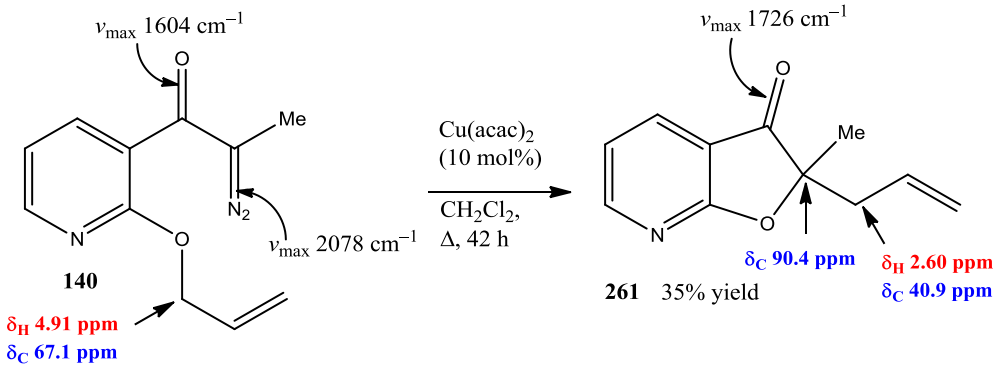
2.4.4.2.2 Transition metal-catalysed reactions of oxygen-containing α-diazoketones

Three oxygen-substituted α-diazoketones **140–142** were synthesised in this work and transition metal-catalysed cyclisations of these compounds was next undertaken. The first substrate investigated was *O*-allyl α-diazoketone **140**. In this case, generation of the [1,4]- or [1,2]-rearrangement products was not anticipated as a significant pathway with the expected reaction pathways likely to involve C–H insertion or oxonium ylide formation/[2,3]-rearrangement (**Scheme 2.129**), as previously described for the analogous phenyl α-diazoketones and α-diazo-β-ketoesters by Pirrung,[259] McKervey[252,253,260] and Mountjoy.[261] In the case of the analogous phenyl systems studied by McKervey *et al.*,[252,253] both the rearrangement and C–H insertion products were detected and the reaction pathways displayed a high degree of catalyst-dependency (**Table 2.17**, entry 1 *vs.* 3).



Scheme 2.129

Reaction of **140** was carried out in the presence of copper(II) acetylacetonate (**Table 2.21**, entry 2) and the reaction mixture was heated under reflux employing Schlenk conditions (**Scheme 2.130**). The reaction was very slow as evidenced by infrared and TLC monitoring and was deemed to be complete after 42 h with infrared spectroscopy and TLC analysis confirming complete reaction of the α-diazoketone **140** and the emergence of a carbonyl peak at ν_{max} 1726 cm^{-1}. Purification by flash chromatography afforded the [2,3]-shift product **261** in 35% yield following rearrangement from the putative oxonium ylide. The characteristic spectroscopic signals for [2,3]-rearrangement product **261** are illustrated below (**Scheme 2.130**).



Scheme 2.130: ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (125.8 MHz, $CDCl_3$) values for 140 and 261

The rearrangement product **261** was identified by ^{1}H NMR spectroscopy, displaying no indication of formation of a C–H insertion product. Characteristic signals for [2,3]-rearrangement product **261** in the ^{1}H NMR spectrum include the methylene signal seen as a doublet of doublets (*J* 7.2, 1.2 Hz) at δ_H 2.60 ppm, in contrast to signals for the α-diazocarbonyl **140** starting material seen as a doublet of triplets (*J* 5.2, 1.6 Hz) at δ_H 4.91 ppm. The ^{13}C NMR spectrum also displayed a shift in the signal for methylene formerly attached to the oxygen atom in the starting material **140**, O<u>C</u>H$_2$CHCH$_2$, from δ_C 67.1 ppm to δ_C 40.9 ppm in the rearrangement product **261**, C(2)<u>C</u>H$_2$CHCH$_2$. The carbon of the newly-formed σ-bond at <u>C</u>(2) was also identified at δ_C 90.4 ppm.

Through comparison of signals in the ^{13}C NMR spectra of **261** and sulfonium ylide/[2,3]-rearrangement product **256**, a clear impact of the heteroatom (O or S) on the chemical shift of the neighbouring carbons was observed (**Figure 2.55**). It was noticeable that carbons in the α-position to the heteroatom were most influenced by this effect. In work by McKervey *et al*.,[253] analysis by ^{13}C NMR spectroscopy showed the signal for <u>C</u>(2) was located at δ_C 84.6 ppm for **262**, whereas the corresponding benzothiophene derivative **258** exhibited a resonance of δ_C 62.1 ppm for the same carbon. The α-substituted quaternary carbon, <u>C</u>(7)a, was located at δ_C 172.8 ppm for **262** and δ_C 151.7 ppm for **258**. It is noteworthy that signals for the bridgehead carbon in the β-position, <u>C</u>(3)a, were unaffected by modification of the heteroatom with similar values of δ_C 131.8 and 130.2 ppm observed for **262** and **258** respectively.

The related pyridine-derived rearrangement products **261** and **256** also exhibited this effect as signals for <u>C</u>(2) were observed at δ_C 90.4 ppm for **261** and at δ_C 63.1 ppm for the sulfur analogue **256** (**Figure 2.55**). However, the α-substituted quaternary carbon, <u>C</u>(7)a, displayed minimal alteration of the chemical shift upon variation of the heteroatom unlike the phenyl rearrangement products **258** and **262**. The signal of δ_C 175.5 ppm for **261** was in close agreement with value of δ_C 173.0 ppm obtained for **256**. This can possibly be rationalised by juxtaposition of the two strongly electronegative atoms to the <u>C</u>(7)a bridgehead carbon, minimising the effect of the α-substituted heteroatom (O or S) on the chemical shift. Incongruously, the quaternary carbon in the β-position to the heteroatom, <u>C</u>(3)a, did exhibit a difference in chemical shift for **261** and **256**. In the ^{13}C NMR spectrum of **261**, the signal for <u>C</u>(3)a was observed at δ_C 113.0 ppm *cf.* δ_C 124.5 ppm for the sulfur rearrangement product **256**.

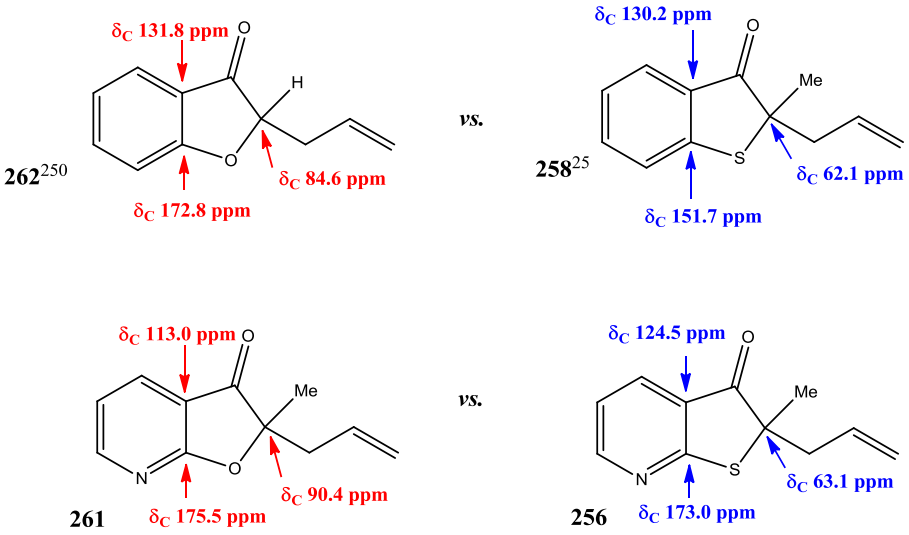
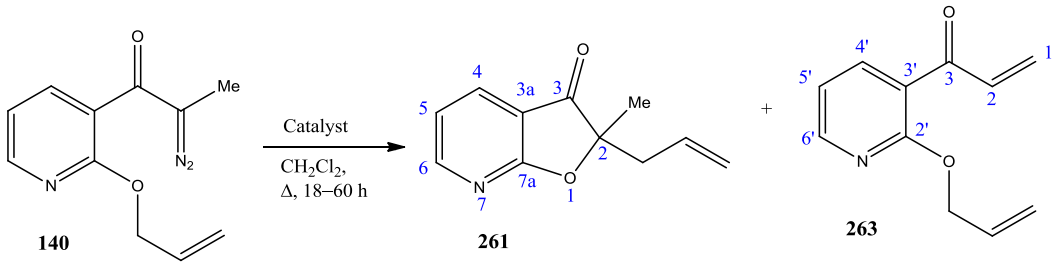


Figure 2.55: Impact of heteroatom on neighbouring carbons in ^{13}C NMR for 262[253] and 258[25] (75.5 MHz, $CDCl_3$) as well as 256 and 261 (125.8 MHz, $CDCl_3$)

Following the successful synthesis of [2,3]-shift product **261** using $Cu(acac)_2$ as catalyst, other copper(II) and rhodium(II) catalysts were investigated for this transformation under the same conditions as previously described. These results are summarised below (**Table 2.20**).

Table 2.21 *Transition metal-catalysed reaction of 1-[2-(allyloxy)pyridin-3-yl]-2-diazopropan-1-one* **140***; oxonium ylide/rearrangement* **261** *and enone formation* **263**[a]



Entry	Catalyst	Time (h)	261 (%)[b]	263 (%)[b]
1	$Cu(hfacac)_2$	60	39[c]	–
2	$Cu(acac)_2$	42	35	–
3	$Rh_2(OAc)_4$	18	–[d]	–
4	$Rh_2(pfb)_4$	18	25[e]	55

[a] Reactions conducted using the general procedure for rhodium(II)- and copper(II)-catalysed C–H insertion and/or ylide formation/rearrangement reactions.

[b] Isolated yields of products after column chromatography.

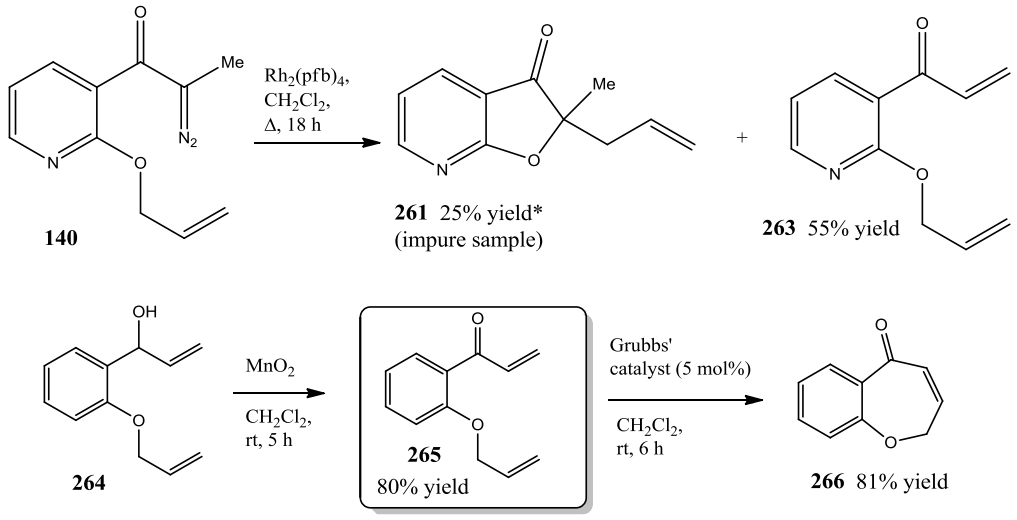
[c] Unknown minor product co-eluted with rearrangement product resulting in a higher yield.

[d] There is possible evidence of 2,3-diketone formation with appearance of a singlet in the ^{1}H NMR of purified product at δ_H 2.46 ppm. However, there is no evidence of formation of **261** or **263.**

[e] Sample isolated is impure and contains a mixture of **261** and an unknown component in essentially equimolar ratio.

The reaction of α-diazoketone **140** in the presence of $Rh_2(OAc)_4$ showed that the starting material was no longer present after 18 h under reflux conditions, as determined by infrared spectroscopy (**Table 2.21**, entry 3). Interestingly, rearrangement product **261** was not detected following chromatography though there was possible evidence for formation of 2,3-diketone. Exposure of **140** to copper(II) hexafluoroacetylacetonate catalyst (**Table 2.21**, entry 1), generated oxonium ylide/rearrangement product **261** in moderate yield, although completion of the reaction required a longer time (60 h) than for the copper(II) acetylacetonate-catalysed reaction.

Finally, and most interestingly, reaction of **140** in the presence of $Rh_2(pfb)_4$ resulted in a golden brown colour in the reaction mixture on addition of catalyst and following chromatography two distinct fractions were isolated (**Table 2.21**, entry 4). The major component isolated was assigned the structure of the terminal enone **263** arising from 1,2-hydride shift while the minor component was recognised as a co-eluting mixture of the [2,3]-shift product **261** and an unknown minor product (**Scheme 2.131**). An analogous phenyl enone **265** was prepared by Li and co-workers from oxidation of the allyl alcohol **264** using MnO_2.[262] The bifunctionalised enone was synthesised for use in ring-closing metathesis (RCM) reactions to prepare a series of substituted benzoxepine derivatives of type **266**.



Scheme 2.131: Cyclisation of 140 in the presence of $Rh_2(pfb)_4$ to afford compounds 261 and 263 and formation of phenyl analogue 265 by Li[262]

Characteristic signals of the terminal enone were observed in the ^{1}H NMR spectrum of **263** including doublets of doublets at δ_H 5.83 ppm (*J* 10.4, 1.6 Hz) and δ_H 6.37 ppm (*J* 17.2, 1.6 Hz), each accounting for one of CHC(1)$\underline{H}_2$, as well as the presence of a broadly split doublet of doublets at δ_H 7.18 ppm (*J* 17.2, 10.4 Hz), corresponding to the α-methine group, C(2)$\underline{H}CH_2$ (**Figure 2.56**). The chemical shifts and splitting pattern observed were in good agreement with data for the phenyl analogue **265** reported by Li (**Figure 2.56**).[262] This was also in good general agreement with terminal enones **237** and **239** investigated earlier in our work (see **Section 2.4.2.2**). Further evidence to support this assignment was obtained by nominal/high resolution mass spectrometry through identification of the molecular ion

$[M+H]^+$ 190.0861. In the ^{13}C NMR spectrum of the terminal enone **263**, the quaternary carbon signal, C(2')OCH_2CHCH_2, was not observed, although the remainder of the signals were assigned.

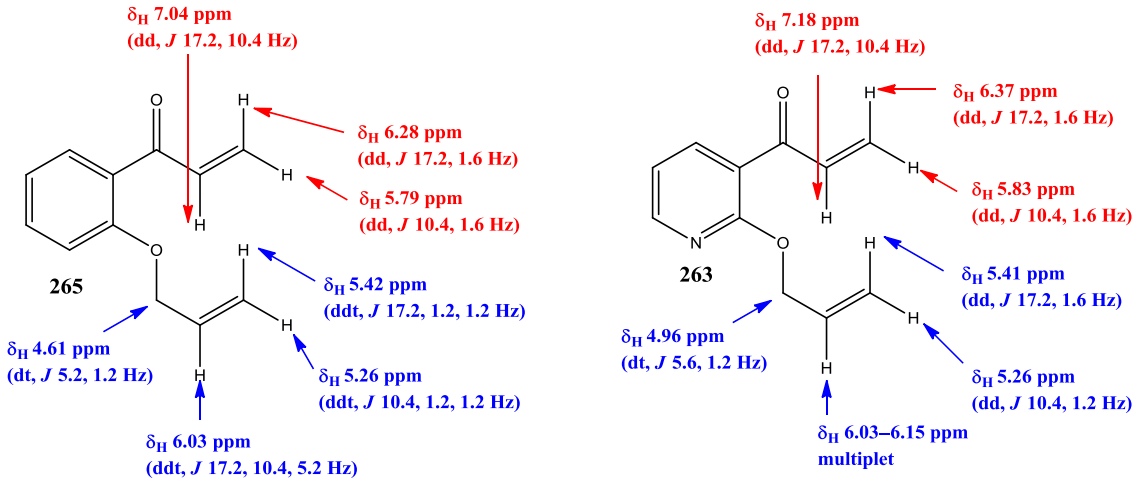


Figure 2.56: Comparison of characteristic ^1H NMR (400 MHz, $CDCl_3$) signals of enone and *O*-allyl ether moieties of 265[262] and 263

The characteristics ^1H NMR signals for both the enone and *O*-allyl ether moieties of compound **263** are illustrated below (**Figure 2.57**).

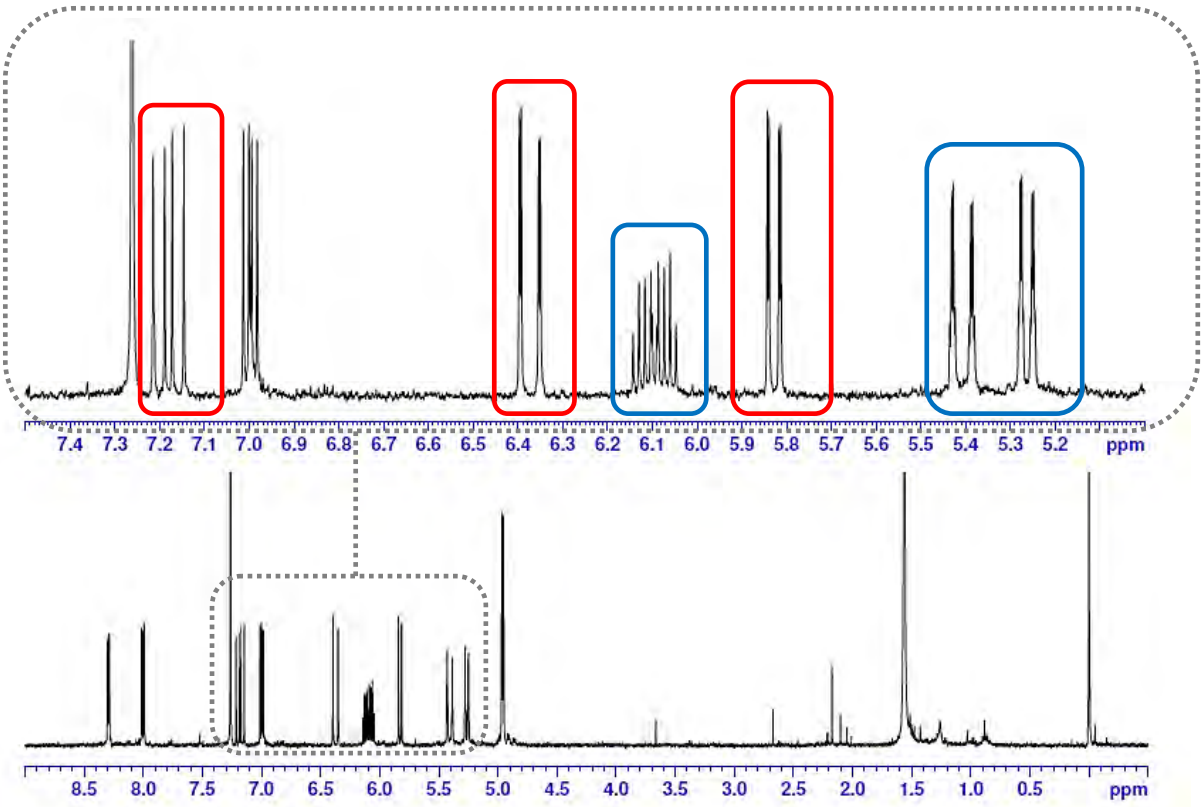


Figure 2.57: ^1H NMR (400 MHz, $CDCl_3$) spectrum and expansion of compound 263. Characteristic signals for the enone moiety are highlighted in red and characteristic peaks for the *O*-allyl ether moiety are highlighted in blue

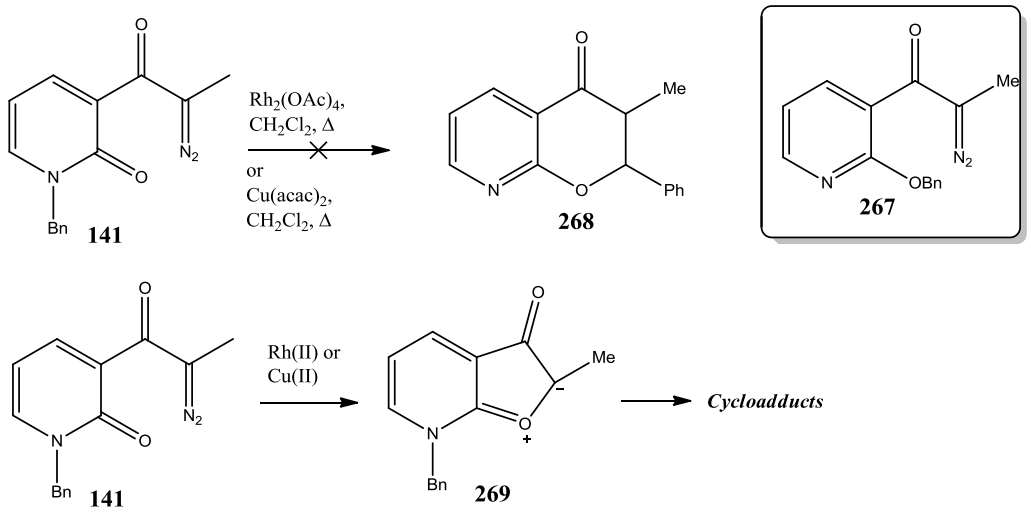
The observation of the 1,2-hydride shift as the major product in the $Rh_2(pfb)_4$-catalysed reaction of **140** is entirely consistent with the outcomes of the reactions of pyridines **134** and **135** (see **Section 2.4.2.2**) where this pathway was again a dominant process. Predominant formation of 1,2-hydride migration products using catalysts possessing strongly electron-withdrawing ligands is in excellent agreement with recent reports by Fox using $Rh_2(tfa)_4$ as catalyst in reactions of cyclic α-diazocarbonyl compounds.[263] This is a significant difference between the pyridyl series and the phenyl series of α-diazoketones; in the phenyl series catalyst such as $Rh_2(tfa)_4$ and $Rh_2(pfb)_4$ favour highly efficient aromatic addition,[11,17] while in the pyridyl series, the 1,2-hydride shift pathway is favoured.

Comparison of the outcomes of the reactions of *O*-allyl pyridyl α-diazoketone **140** and the *O*-allyl phenyl analogue **247** (**Scheme 2.117**) is very interesting. In the phenyl series, rhodium catalysis leads to C–H insertion while copper catalysis leads to oxonium ylide formation/[2,3]-rearrangement. In the pyridyl series, use of copper catalysis favours [2,3]-rearrangement product, while use of $Rh_2(pfb)_4$ leads to predominant formation of the 1,2-hydride shift product **263** with [2,3]-rearrangement observed as a minor pathway.

Following successful ylide formation/rearrangement of pyridine-containing α-diazoketones **140**, **143** and **144**, potential C–H insertion reactions of α-diazocarbonyl compounds **141** and **142** were next explored. To the best of our knowledge, intramolecular C–H insertions have not been described for pyridine α-diazoketones. Previous work for the phenyl analogues using rhodium and copper catalysts, as described by McKervey *et al.* resulted in the formation of chromanones arising from C–H insertion.[252,253] To complement these results, benzyl and ethyl substituted pyridine α-diazoketones **141** and **142** were examined to ascertain if the reaction pathways of the pyridine systems parallels those exhibited by the phenyl series.

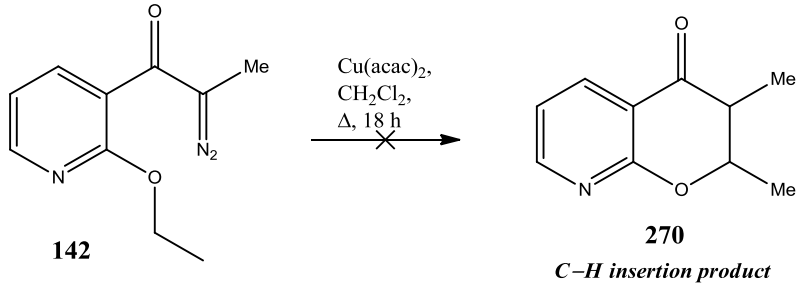
The benzyl substituted derivative **141** was the first substrate investigated with the reaction carried out using $Rh_2(OAc)_4$ and $Cu(acac)_2$ catalysts respectively (**Scheme 2.132**) (at the time, the structure of **141** was thought to be **267** but this was later corrected). For the reactions involving $Rh_2(OAc)_4$ and $Cu(acac)_2$, no identifiable products were isolated in either experiment. Following this, no further transition metal-catalysed reactions of **141** was attempted as limited amounts of this compound were available.

As the benzyl substituted compound was in fact the *N*-benzyl derivative **141** and not the *O*-benzyl derivative **267** as originally assumed, this meant that a C–H insertion pathway resulting in formation of **268** is not possible and the reaction pathway presumably involved generation of a carbonyl ylide **269**, which could potentially be intercepted by a dipolarophile in a 1,3-dipolar cycloaddition.



Scheme 2.132

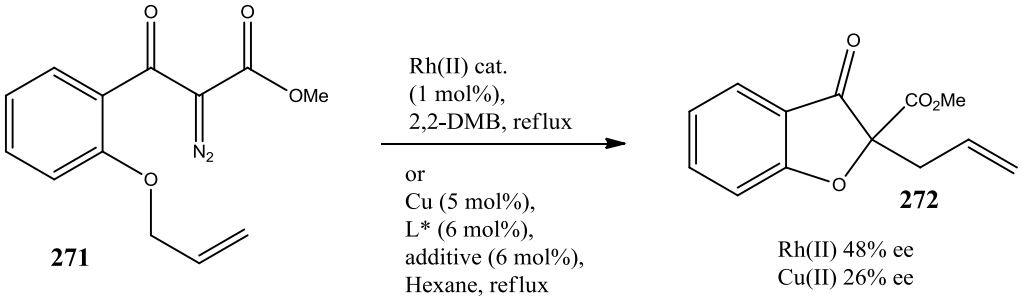
While the *N*-ethyl acid **124** was prepared in the synthesis of α-diazoketone **142**, interestingly it appears the *O*-ethyl α-diazoketone **142** is the isolated compound using the acylation approach (see **Section 2.3.1.5.1**). Due to the limited amount of **142** synthesised, only one attempted cyclisation was carried out with copper(II) acetylacetonate as catalyst for this transformation (**Scheme 2.133**). Analysis by infrared spectroscopy indicated that the reaction was complete after heating under reflux for 18 h. However, following chromatography, no identifiable products were isolated. No further transition metal-mediated processes were attempted on α-diazoketone **142**, due to lack of sample.



Scheme 2.133

Attempted C–H insertion reactions were unsuccessful in this work, however, the allyl substituted oxonium and sulfonium ylides generated the expected [2,3]-rearrangement products in good yields when copper(II) catalysts were employed. In addition, formation/rearrangement of oxonium and sulfonium ylides from transformations of pyridine-containing α-diazoketones has not been previously described and these are the first examples of such processes for this type of novel substrate. This robust method opens up the possibility of enantioselective copper-mediated catalysis utilising *O*-allyl and *S*-allyl α-diazoketones **140** and **144**. A range of chiral copper complexes has proven very useful for a variety of enantioselective transformations in the Maguire research group and use of these catalysts in conjunction with the pyridine systems may be investigated in future work.

Recently, Slattery carried out oxonium ylide/[2,3]-rearrangement reactions on a related phenyl substrate **271** using copper(II) chloride allied with a variety of chiral bis(oxazoline) ligands and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (NaBARF), although low enantiopurities were obtained for this process (**Scheme 2.134**).[264] Reaction of **271** with chiral rhodium(II) catalysts using 2,2,dimethylbutane (2,2-DMB) provided moderate to good ee's for [2,3]-rearrangement product **272**. As the application of chiral rhodium(II) carboxylates with *O*-allyl and *S*-allyl α-diazoketones **140** and **144** is unexplored, this presents an opportunity for detailed catalyst studies in the rearrangement processes.



Scheme 2.134

2.4.5 Cyclopropanation

2.4.5.1 Background

The intermolecular cyclopropanation of styrene by α-diazoketones and α-diazo-β-ketoesters was the last series of reaction pathways investigated. Davies has reported cyclopropanations for pyridine systems of general type **273**, with the main difference that these systems are donor/accetor carbenoids, as described by Davies' classification (**Figure 2.58**).[33] This would indicate that compounds in this project of general structure **274** possess a different reactivity profile and are probably categorised as acceptor carbenoids using α-diazoketones and acceptor/acceptor carbenoids when α-diazo-β-ketoesters are used as precursors to the carbenoids. Moreover, this suggests that the acceptor and acceptor/acceptor carbenoid precursors **274** may not be as applicable towards intermolecular cyclopropanation as Davies' counterparts **273**, where the electron-donating group (vinyl, alkynyl, aryl or heteroaryl) stabilises the metallocarbenoid through resonance, resulting in enhanced stability and chemoselectivity.

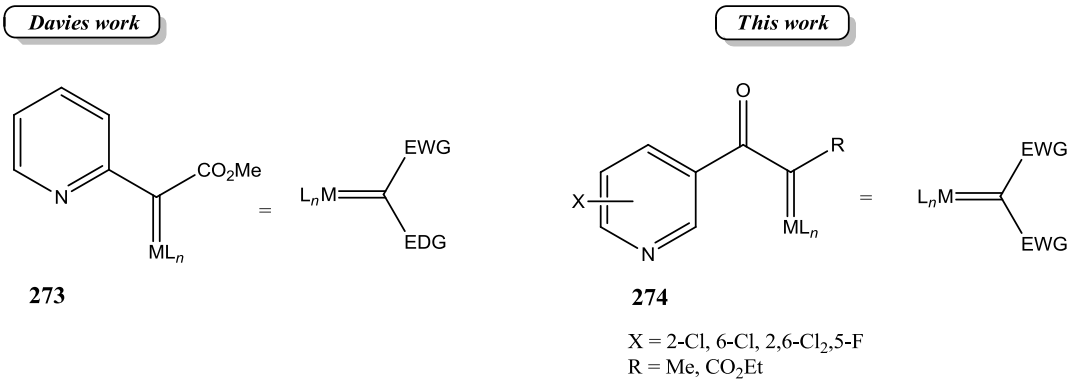
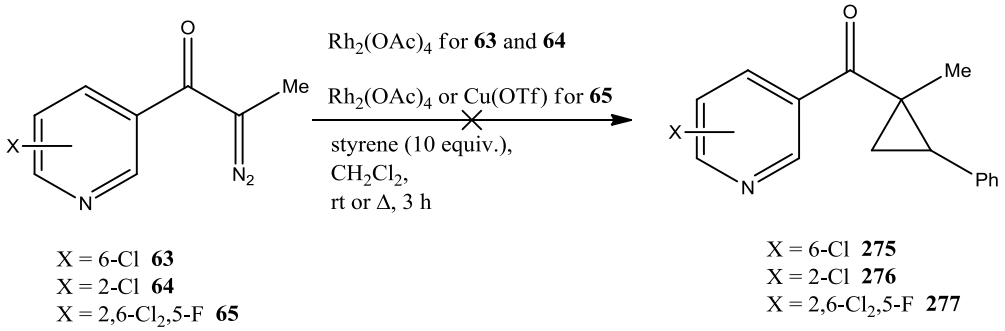


Figure 2.58: Comparison between substrates 273 used by Davies[33] and 274 employed in the current investigation

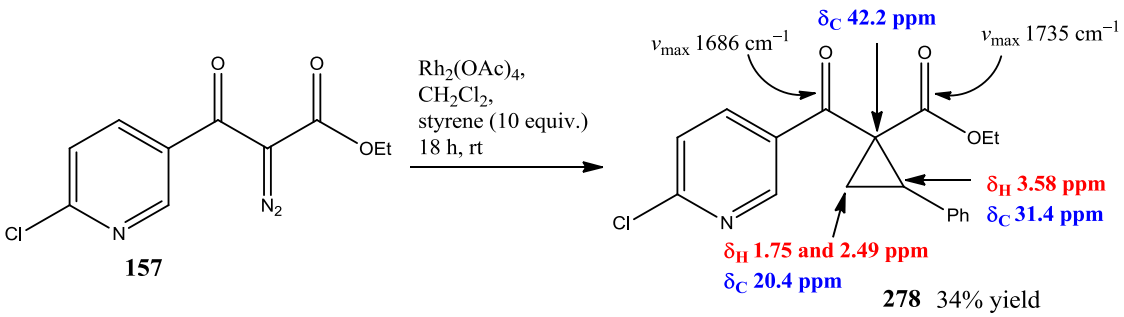
2.4.5.2 Intermolecular cyclopropanation of pyridine-containing α-diazocarbonyl compounds

Initial efforts focused on attempted cyclopropanation of styrene with each of pyridyl α-diazoketones, **63** and **64** in the presence of rhodium(II) acetate and styrene (10 equiv.) in doubly distilled dichloromethane (**Scheme 2.135**). However, there was no appreciable formation of the corresponding cyclopropane **276** in the reaction of **64**. Interestingly, reaction of α-diazoketone **63** in the presence of rhodium(II) acetate tentatively indicated formation of the cyclopropane **275** by identification of characteristic signals for the cyclopropane ring in the ^{1}H NMR spectrum of the crude product. Following column chromatography, the purified product was not isolated cleanly and the compound still contained a large amount of signals in the high-field region of the spectrum. The next substrate examined was α-diazoketone **65**, which was treated with both rhodium(II) acetate and copper(II) triflate as catalysts for the cyclopropanation (**Scheme 2.135**). Characteristic cyclopropane signals for **277**, as well as signals for the 2,3-diketone were identified in the crude ^{1}H NMR spectrum, but following purification, a clean sample of the product could not be obtained. Some evidence of the 1,2-hydride shift was also seen in the ^{1}H NMR of these reactions.



Scheme 2.135

As the α-diazoketone systems **63-65** did not appear to undergo cyclopropanation easily, α-diazo-β-ketoesters were explored as potential substrates for intermolecular cyclopropanation and α-diazo-β-ketoester **157** was initially examined for this process (**Scheme 2.136**).



Scheme 2.136

The cyclopropanation was carried out under Schlenk conditions and following monitoring by infrared and TLC analysis after 18 h, the reaction was determined to have gone mostly to completion, although a small amount of unreacted α-diazo-β-ketoester **157** still appeared to be present by infrared spectroscopy. Following purification by column chromatography, ^{1}H NMR spectroscopic analysis indicated formation of the cyclopropane, however, isolation of a clean sample of the desired product proved challenging as the sample still contained a significant amount of signals in the high-field region of the spectrum. Eventually, purification was achieved *via* crystallisation using a slow evaporation from dichloromethane and hexane. After 48 h, a white solid was afforded which was identified as the purified cyclopropanation product **278**, isolated in 34% yield. Structural identity was confirmed by the characteristic cyclopropane signals in the ^{1}H NMR spectrum, identified as three doublets of doublets at δ_H 1.75 (*J* 9.3, 5.1 Hz), 2.49 (*J* 8.1, 4.8 Hz) and δ_H 3.58 (*J* 9.0, 8.4 Hz) ppm (**Scheme 2.136**). In addition, characteristic ^{13}C NMR signals for the cyclopropane were seen at δ_C 20.4, 31.4 and 42.2 ppm, aiding confirmation of cyclopropane **278** (**Scheme 2.136**). These values were in very good agreement with ^{1}H and ^{13}C NMR properties described for analogous cyclopropane **279** prepared by Charette:[244] δ_H 1.64 (*J* 9.1, 4.9 Hz), 2.42 (*J* 8.1, 4.9 Hz), 3.52 (*J* 8.5 Hz) ppm and δ_C 19.6, 30.4, 42.1 ppm. Further characterisation including infrared spectroscopy, as well as nominal and high resolution mass spectrometry was undertaken. Elemental analysis was attempted on compound **278** but this did not give a value within the defined parameters.

It should also be noted that the minor isomer was present in a small amount (~16 mol%), though it is uncertain at this point whether the *cis* or *trans* is the predominant isomer. By comparison with ^{1}H and ^{13}C NMR spectroscopic data described for *cis gem*-dicarbonyl substituted cyclopropane **279** in the literature,[244] a tentative assignment of the *cis* isomer as the major component is possible, however, the definitive configuration remains uncertain in this case. The ^{1}H NMR spectrum of cyclopropane **278** highlighting the signals assigned to the major and minor isomers is shown below (**Figure 2.59**).

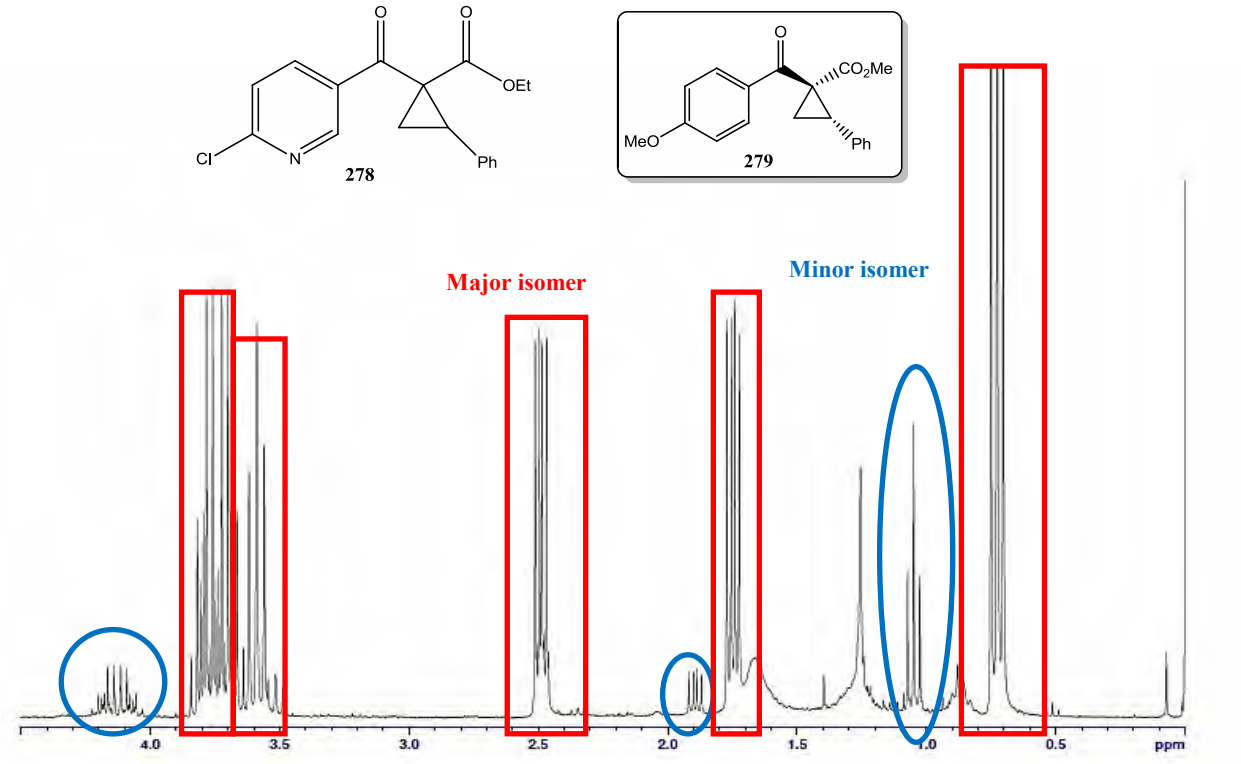
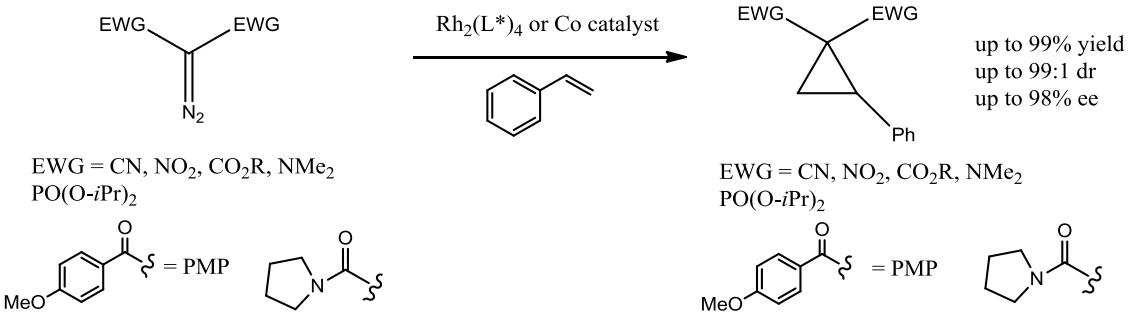


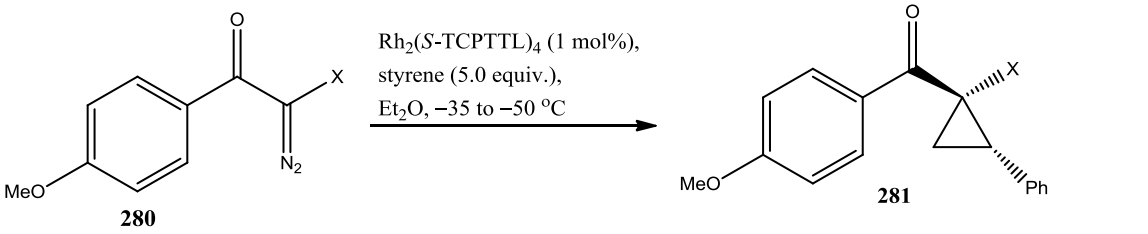
Figure 2.59: Expansion of ^{1}H NMR (300 MHz, $CDCl_3$) spectrum of cyclopropane 278 highlighting characteristic cyclopropane peaks

In the previous decade, Charette,[244,265-270] Zhang[271,272] and Doyle[273] have reported significant progress in synthesis of *gem*-diacceptor cyclopropanes posessing α-nitro-, α-cyano-, α-amido-, α-aceto- and α-phosphonate acceptor groups *via* intermolecular cyclopropanation of alkenes by diacceptor diazo precursors (**Scheme 2.137**). Charette has discussed a '*trans* directing effect' (9 : 1 to >30 : 1 dr) for α-amido-containing diacceptor diazo compounds based on the strategy of generating a metallocarbenoid containing two carboxy groups of different '*trans* directing abilities'. It is noteworthy in Charette's work with the *gem*-dicarboxy cyclopropanes that the *cis* designation arises from the orientation of the phenyl ring with respect to the ester moiety. Interestingly, further work by the same group employing a *para*-methoxyphenyl (PMP) substrate preferentially generated the *cis* *gem*-diacceptor cyclopropanes (up to 99 : 1 dr).



Scheme 2.137

However, very limited reports have been disclosed for intermolecular cyclopropanation of *gem*-dicarbonyl diazo compounds of type **280** (X = CO_2Me) until investigations by Charette in 2011 using a PMP stereocontrolling group (**Scheme 2.138**).[244] In that work, the acceptor/acceptor diazo system was allied with the Rh_2(*S*-TCPTTL)$_4$ catalyst to provide the enantioenriched *cis gem*-diacceptor cyclopropanes **281**, while the absolute configuration was determined by X-ray crystallography of the cyclopropane products.



280

X = NO_2, CN, CO_2Me

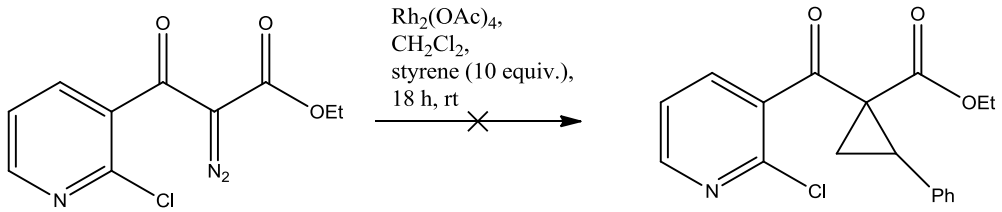
281

X = NO_2 81% yield, 98:2 dr 93% ee (*cis*)
X = CN 98% yield, 95:5 dr 84% ee (*cis*)
X = CO_2Me 60% yield 99:1 dr 88% ee (*cis*)

Scheme 2.138

The brief literature overview places the successful intermolecular cyclopropanation of styrene using pyridine diacceptor diazo compound **157** in context and this appears to be the first example of a *gem*-diacceptor cyclopropane bearing a pyridine ring *via* transition metal catalysis. While Davies has previously reported intermolecular cyclopropanations using pyridine α-diazoacetates of type **273**,[33] the current work allows investigation of a different group of metallocarbenoids possessing different reactivity profiles. Asymmetric intermolecular cyclopropanations of the pyridine *gem*-diacceptor compound **157** is also possible and may be investigated in future work.

The intermolecular cyclopropanation of styrene was also attempted using ethyl 3-(2-chloropyridin-3-yl)-2-diazo-3-oxopropanoate **158**. However, reaction of **158** in the presence of rhodium(II) acetate did not appear to generate the cyclopropane product **282** (**Scheme 2.139**).



158 **282**

Scheme 2.139

No further intermolecular cyclopropanations were attempted in this project but these results indicate that pyridine-containing α-diazo-β-ketoesters appear to be more suitable for this type of reaction than the corresponding α-diazoketones. It is noteworthy that even when the cyclopropanes were successfully synthesised as determined by ^{1}H NMR spectroscopy, isolating analytically pure cyclopropanes from the complex mixtures proved challenging. This

presents an opportunity to improve this technique to ease the isolation of clean samples of the cyclopropane products. However, successful synthesis of cyclopropane **278** represents the first reported synthesis of *gem*-diacceptor cyclopropanes possessing a pyridine ring, which potentially allows stereoselective access to a series of novel pyridine-containing cyclopropanes.

2.5 Conclusions

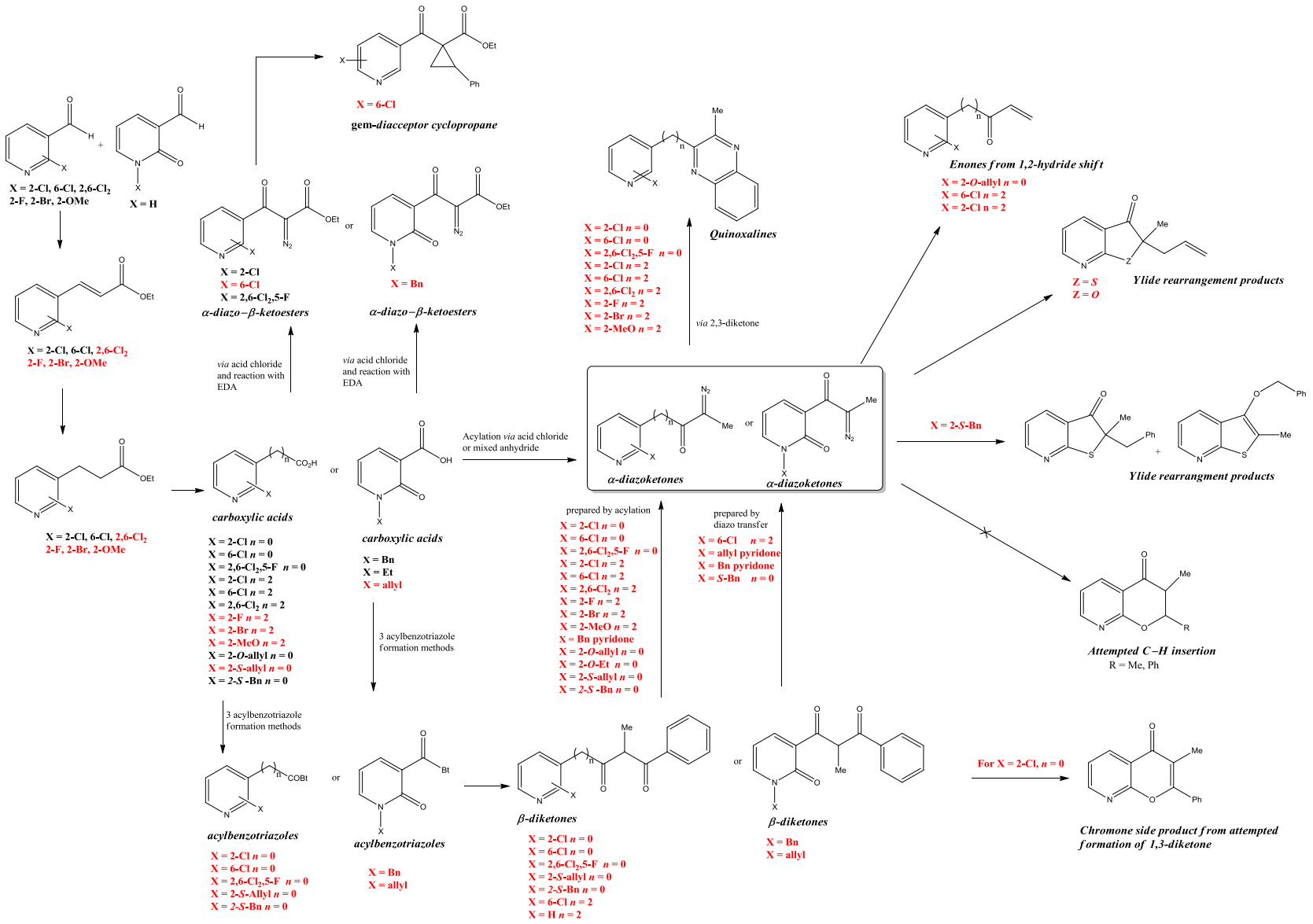
- In the course of this work, it has been demonstrated that preparation of pyridine-containing α-diazoketones is possible by two principal methods; acylation of diazoalkanes using acid chlorides and unsymmetrical anhydrides facilitated through modification of the electronic properties of the ring, or by means of a complementary method employing debenzoylation diazo transfer. Prior to this, little formal recognition of the importance of electron-withdrawing groups in the formation of pyridine acid chlorides has been discussed in the literature. In addition, pyridyl α-diazo-β-ketoesters were successfully prepared in one-pot by reaction of an acid chloride with ethyl diazoacetate.

- The diazo transfer method, along with initial steps to synthesise the acylbenzotriazole and β-diketone precursors certainly leave room for optimisation of these procedures as the yields obtained are significantly lower than for the phenyl analogues. Improvements in these synthetic steps can enable the debenzoylation diazo transfer to be viewed as a viable alternative to prepare internal α-diazoketones.

- The reactions of pyridine-containing α-diazocarbonyl compounds are sparsely studied in the literature and this work has significantly augmented the knowledge of these transformations. Transition metal-mediated processes of the pyridyl α-diazoketones in this work have shown some interesting trends; formation of 2,3-diketones *via* oxidation is highly favoured in systems where no other reaction pathways are predominant, although strict control of conditions can tend to favour a pathway leading to enones, generated *via* 1,2-hydride shift. Through the tethering of *O*- and *S*-alkyl or aryl groups on the pyridine α-diazoketones, it has been demonstrated that ylide formation/rearrangement involving both oxonium and sufonium ylides can be accomplished using a targeted substrate design. Moreover, successful preparation of oxonium and sulfonium ylide/rearrangement products opens a conduit to future asymmetric syntheses of these compounds, as well as broadening the scope within the Maguire research group for such transformations. The reactivity of the pyridyl α-diazoketones has also been contrasted with the reactivity of the analogous phenyl derivatives. In particular, while aromatic addition is a favoured reaction pathway with the phenyl derivatives, no evidence of addition to the pyridine ring has been detected in this work.

- A comprehensive series of novel pyridine-containing compounds have been synthesised during this project including esters, carboxylic acids, acylbenzotriazoles, 1,3-diketones, 2,3-diketones, α-diazoketones, α-diazo-β-ketoesters, quinoxalines, enones arising from 1,2-hydride shift, cyclopropanes and ylide formation/rearrangement products. Compounds previously identified, but not fully characterised have been fully characterised in this project, providing a more definitive set of associated spectral and physical properties. A total of 12 X-ray crystal structures were obtained during the synthetic efforts (for full data see *Appendix II*). An overall representation of the synthetic work undertaken in this chapter, including all novel compounds (highlighted in red) prepared is displayed below (**Scheme 2.140**). The potential for biological activity in this broad series of compounds is significant and may be explored in future work.

- This work illustrates that in spite of their innate basicity, pyridine substrates can serve as useful templates for the generation of novel heterocyclic α-diazoketones. Through further investigation, the structural design and reactivity of these systems can be better understood, offering an advantageous position for the synthesis of a broad range of novel heterocyclic compounds.


X = 2-Cl, 6-Cl, 2,6-Cl2
2-F, 2-Br, 2-OMe
X = H
X = 6-Cl
gem-diacceptor cyclopropane
X = 2-Cl
X = 6-Cl
X = 2,6-Cl2,5-F
α-diazo−β-ketoesters
X = Bn
α-diazo−β-ketoesters
X = 2-Cl, 6-Cl, 2,6-Cl2
2-F, 2-Br, 2-OMe
via acid chloride and reaction with EDA
via acid chloride and reaction with EDA
X = 2-Cl, 6-Cl, 2,6-Cl2
2-F, 2-Br, 2-OMe
carboxylic acids
X = 2-Cl n = 0
X = 6-Cl n = 0
X = 2,6-Cl2,5-F n = 0
X = 2-Cl n = 2
X = 6-Cl n = 2
X = 2,6-Cl2 n = 2
X = 2-F n = 2
X = 2-Br n = 2
X = 2-MeO n = 2
X = 2-O-allyl n = 0
X = 2-S-allyl n = 0
X = 2-S -Bn n = 0
carboxylic acids
X = Bn
X = Et
X = allyl
Acylation via acid chloride or mixed anhydride
3 acylbenzotriazole formation methods
3 acylbenzotriazole formation methods
acylbenzotriazoles
X = 2-Cl n = 0
X = 6-Cl n = 0
X = 2,6-Cl2,5-F n = 0
X = 2-S-Allyl n = 0
X = 2-S-Bn n = 0
acylbenzotriazoles
X = Bn
X = allyl
α-diazoketones
α-diazoketones
prepared by acylation
X = 2-Cl n = 0
X = 6-Cl n = 0
X = 2,6-Cl2,5-F n = 0
X = 2-Cl n = 2
X = 6-Cl n = 2
X = 2,6-Cl2 n = 2
X = 2-F n = 2
X = 2-Br n = 2
X = 2-MeO n = 2
X = Bn pyridone
X = 2-O-allyl n = 0
X = 2-O-Et n = 0
X = 2-S-allyl n = 0
X = 2-S -Bn n = 0
prepared by diazo transfer
X = 6-Cl n = 2
X = allyl pyridone
X = Bn pyridone
X = S-Bn n = 0
β-diketones
X = 2-Cl n = 0
X = 6-Cl n = 0
X = 2,6-Cl2,5-F n = 0
X = 2-S-allyl n = 0
X = 2-S-Bn n = 0
X = 6-Cl n = 2
X = H n = 2
β-diketones
X = Bn
X = allyl
Quinoxalines
X = 2-Cl n = 0
X = 6-Cl n = 0
X = 2,6-Cl2,5-F n = 0
X = 2-Cl n = 2
X = 6-Cl n = 2
X = 2,6-Cl2 n = 2
X = 2-F n = 2
X = 2-Br n = 2
X = 2-MeO n = 2
via 2,3-diketone
Enones from 1,2-hydride shift
X = 2-O-allyl n = 0
X = 6-Cl n = 2
X = 2-Cl n = 2
Z = S
Z = O
Ylide rearrangement products
X = 2-S-Bn
Ylide rearrangment products
Attempted C−H insertion
R = Me, Ph
For X = 2-Cl, n = 0
Chromone side product from attempted formation of 1,3-diketone

Scheme 2.140

2.6 General procedures and Experimental

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorous pentoxide[274] and when used for transformations of α-diazocarbonyl compounds was further distilled from calcium hydride[275] and stored over activated 4 Å molecular sieves; ethyl acetate was distilled from potassium carbonate;[275,276] hexane was distilled prior to use; ethanol and methanol were distilled from the corresponding magnesium alkoxide (stored over 3 Å molecular sieves).[275] Toluene was distilled from sodium and benzophenone and stored over 4 Å molecular sieves; tetrahydrofuran (THF) was distilled from sodium and benzophenone; acetonitrile was distilled over calcium hydride and stored over activated 4 Å molecular sieves. Diisopropylamine was distilled from calcium hydride. Molecular sieves were dried by heating at 150 °C overnight. Organic phases were dried using anhydrous magnesium sulfate. Diethyl ether is referred to as ether throughout. All reagents were used without further purification except for diaminobenzene which was purified by recrystallisation from hot dichloromethane, followed by charcoal treatment and hot filtration.[231] All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated.

Diazomethane was generated from Diazald® in glassware containing clear glass joints.[277] Trimethylsilyldiazomethane ($TMSCHN_2$) is also used a source of diazomethane.

Dr Alan Ford prepared the chiral dirhodium catalysts[167] and Johnson Matthey kindly provided the rhodium acetate dimer.

In the case of previously prepared compounds, ^{1}H NMR spectra, infrared spectra and melting point (m.p.) analysis were carried out. In instances where the compound was novel ^{13}C NMR, LRMS, HRMS were recorded and elemental analysis where feasible.

Infrared spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids on a Perkin Elmer Paragon 1000 FT-IR spectrometer.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. ^{1}H (500 MHz) and ^{13}C (125.8 MHz) NMR spectra were recorded on a Bruker Avance 500 MHz NMR spectrometer. ^{1}H (600 MHz) and ^{13}C (150.9 MHz) NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer. All spectra were recorded at room temperature (~20 °C) in deuterated chloroform ($CDCl_3$) unless otherwise stated using tetramethylsilane (TMS) as an internal chemical shift reference standard. ^{1}H NMR spectra recorded in deuterated dimethylsulfoxide (DMSO-d_6) were assigned using the DMSO peak as the internal chemical shift reference standard. ^{19}F NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer at 376.5 MHz in both proton coupled mode and proton decoupled mode. All the spectra were recorded at ~20 °C in deuterated chloroform ($CDCl_3$) unless otherwise stated, using hexafluorobenzene as the internal chemical shift reference standard (~0.0001%) with the standard signal recalibrated to 0 ppm. Chemical shifts (δ_H & δ_C) are reported in parts per million (ppm) and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H, ^{19}F and ^{13}C spectra are designated as s (singlet), br s (broad singlet), br d (broad doublet), br t (broad triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets) and m (multiplet). ^{13}C NMR spectra were assigned with the

aid of DEPT experiments. Compounds which were assigned with the aid of DEPT experiments were listed by identifying both the carbon, (CH_3, CH_2, CH or C) and also the atom number of the carbon, for example [CH_3, $\underline{C}(3)H_3$]. ^{13}C NMR spectra were calibrated using solvent signals *i.e.* $CDCl_3$: δ_C 77.0 ppm, DMSO-d_6: δ_C 39.5 ppm. On occasion, *J* values measured from the spectra do not exactly match up, but always fall within experimental error. The values recorded are those that are measured. All spectroscopic details for known compounds were in agreement with those previously reported unless otherwise stated.

Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer in electrospray ionisation (ESI) mode and high resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer in electrospray ionisation (ESI) mode. The samples were made up in acetonitrile using 50% water/acetonitrile containing 0.1% formic acid as eluent.

Elemental analyses were performed by the Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

Melting points were carried out on a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected.

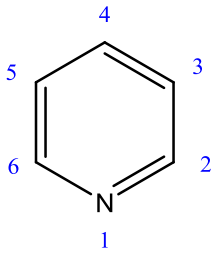
Flash chromatography was performed using Kieselgel silica gel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV (254nm) detection, iodine staining, vanillin staining, ceric staining or phosphomolybdic acid staining.

Microwave assisted synthesis was carried out using the CEM Discover Labmate Synthesiser in conjunction with ChemDriver software (Version 3.5.0) and the CEM Discover S-Class Synthesiser in conjunction with Synergy software.

Single crystal X-ray analysis was conducted by Dr S. E. Lawrence and Dr Kevin Eccles, Department of Chemistry, National University of Ireland, Cork, using a Bruker APEX II DUO diffractometer or a Bruker SMART X2S diffractometer,[278] at temperature 100 K using graphite monochromatic Mo Kα (λ = 0.7107 A) radiation fitted with an Oxford Cryosystems Cobra-low-temperature device. All calculations and refinement were made using APEX software.[279] The structures were solved using direct methods and refined on F^2 using SHELXL-97. Analysis was undertaken with the SHELX suite of programmes and diagrams prepared with Mercury 3.0.[280] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were located and refined with isotropic thermal parameters.

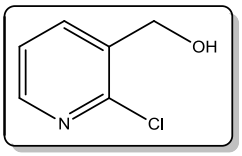
Enantiopurities were determined by chiral stationary phase high performance liquid chromatography (HPLC) performed on a Chiralpak® OJ-H or Chiralcel® OD-H column. Details of the column conditions and mobile phases employed are included in *appendix III*. HPLC analysis was performed on a Waters alliance 2690 separations module. All chiral columns were purchased from Daicel Chemical Industries Limited. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^T$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}.

Synthesis of functionalised alcohols and aldehydes



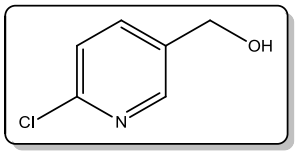
Numbering scheme for Pyridines

(2-Chloropyridin-3-yl)methanol 66[70]



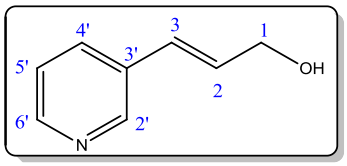
2-Chloronicotinic acid **57** (12.50 g, 78.90 mmol) and thionyl chloride (50 mL, 685 mmol) were heated under reflux for 2 h and subsequently concentrated to afford the crude *acid chloride* as a yellow solid. The acid chloride was dissolved in tetrahydrofuran (40 mL) and added dropwise over 30 min to a stirring solution of sodium borohydride ($NaBH_4$) (12.50 g, 78.90 mmol) in water (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min; then the mixture was diluted with brine (30 mL) and extracted with ether (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated to yield the crude *alcohol* **66** (10.12 g, 89%) as a white solid; m.p. 61 °C (lit.,[70] 62–63 °C); ν_{max}/cm^{-1} (KBr) 3402, 1623, 1577, 1409, 1049. 800, 712; δ_H (300 MHz, $CDCl_3$) 4.80 [2H, s, C$\underline{H}_2$OH], 7.30 [1H, dd, *J* 4.8, 2.8, C(5)$\underline{H}$], 7.93 [1H, dt, *J* 1.6, 0.8, C(4)$\underline{H}$], 8.30 [1H, br d, *J* 2.8, C(6)$\underline{H}$]. Spectral characteristics were consistent with previously reported data.[70]

(6-Chloropyridin-3-yl)methanol 67[78,104]



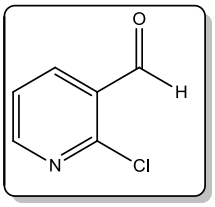
6-Chloronicotinoyl chloride **60** (13.89 g, 78.90 mmol) was dissolved in tetrahydrofuran (40 mL) and added dropwise over 30 min to a stirring solution of sodium borohydride (12.50 g, 78.90 mmol) in water (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min; then the mixture was diluted with brine (30 mL) and extracted with ether (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated to yield the crude *alcohol* **67** (10.21 g, 90%) as a white solid; m.p. 61–62 °C (lit.,[104] 63–65 °C); ν_{max}/cm^{-1} (KBr) 3352, 2873, 1590, 1571, 1460, 1388, 1105, 1022; δ_H (400 MHz, $CDCl_3$) 3.37 [1H, br s, O$\underline{H}$], 4.71 [2H, s, C$\underline{H}_2$OH], 7.31 [1H, d, *J* 8.0, C(5)$\underline{H}$], 7.69 [1H, dd, *J* 8.4, 2.4, C(4)$\underline{H}$], 8.30 [1H, d, *J* 2.4, C(2)$\underline{H}$]. Spectral characteristics were consistent with previously reported data.[78]

(*E*)-3-(Pyridin-3-yl)prop-2-en-1-ol 154[160]



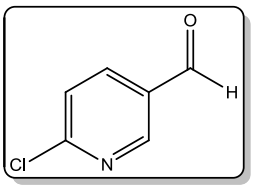
Pyridine acrylate ester **41** (6.05 g, 34.2 mmol) was dissolved in ether (100 mL) and stirred at –40 °C. A solution of diisobutylaluminium hydride [(DIBAl-H), (1.0 M in hexanes, 68.3 mL, 68.30 mmol)] was added dropwise to the reaction mixture. A bright yellow colour was observed on initial addition of DIBAl-H, and then subsequently changed to a dark red colour on complete addition of DIBAl-H. The reaction mixture was stirred at room temperature overnight and then cooled to 0 °C. Water (15 mL), aqueous sodium hydroxide (1.0 M, 15 mL) and water (20 mL) were sequentially added; then the mixture was stirred for 2 h at room temperature. Suction filtration of the semi-solid aqueous layer followed by concentration under reduced pressure gave the crude *alcohol* as viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) to ethyl acetate/triethylamine (99.9:0.1) generated the pure *alcohol* **154** (0.79 g, 17%) as an orange oil; ν_{max}/cm^{-1} (film) 3293, 2852, 1657, 1591, 1574, 1482, 1418, 1091, 1026, 970, 706; δ_H (400 MHz, $CDCl_3$) 4.35 [2H, dd, *J* 5.2, 1.2, C(1)$\underline{H}_2$OH], 6.43 [1H, dt, *J* 16.0, 4.8, C(2)$\underline{H}CH_2OH$], 6.60 [1H, d, *J* 16.0, C(3)$\underline{H}$], 7.22 [1H, dd, *J* 8.0, 4.8, C(5')$\underline{H}$], 7.68 [1H, d with further unresolved splitting, *J* 8.0, C(4')$\underline{H}$], 8.39 [1H, d with further unresolved splitting, *J* 4.8, C(6')$\underline{H}$], 8.51 [1H, s, C(2')$\underline{H}$]. Spectral properties were consistent with previously reported data.[160]

2-Chloronicotinaldehyde 68[70,72]



Pyridine chlorochromate [(PCC), (13.88 g, 64.4 mmol)] was added portionwise to a solution of alcohol **66** (7.71 g, 53.6 mmol) in doubly distilled dichloromethane (80 mL) at 0 °C. On addition of PCC, the colour of the reaction mixture turned from yellow to black. The reaction mixture was stirred for 2 h at room temperature. Dilution with ether (3 × 60 mL), subsequent filtration through a pad of Celite® and concentration under reduced pressure afforded the crude *aldehyde* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *aldehyde* **68** (3.80 g, 50%) as a white solid; m.p. 48–50 °C (lit.,[72] 50 °C); ν_{max}/cm^{-1} (KBr) 2911, 1696, 1660, 1580, 1418, 1379, 1264, 1069; δ_H (400 MHz, $CDCl_3$) 7.44 [1H, dd, *J* 7.6, 4.8, C(5)$\underline{H}$], 8.25 [1H, dd, *J* 7.6, 2.0, C(4)$\underline{H}$], 8.62 [1H, dd, *J* 4.8, 2.0, C(6)$\underline{H}$], 10.46 [1H, s, C$\underline{H}$O]. Spectral properties were consistent with previously reported data.[70]

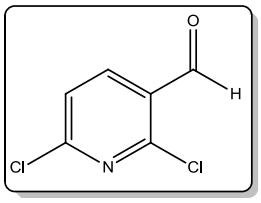
6-Chloronicotinaldehyde 69[78,79,281]



This was prepared following the procedure described for **68**, from a solution of alcohol **67** (10.21 g, 71.13 mmol) in doubly distilled dichloromethane (80 mL) and PCC (18.39 g, 85.3 mmol) to afford the crude *aldehyde* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *aldehyde* **69** (5.13 g, 51%) as a white solid; m.p. 75–76 °C (lit.,[79] 70–71°C); ν_{max}/cm^{-1} (KBr) 2920, 1702, 1654, 1638, 1590, 1561, 1459, 1354, 1112, 833; δ_H (400 MHz, $CDCl_3$) 7.52 [1H, d, *J* 8.4, C(5)$\underline{H}$], 8.14 [1H, dd, *J* 8.4, 2.4, C(4)$\underline{H}$], 8.87 [1H, d, *J*

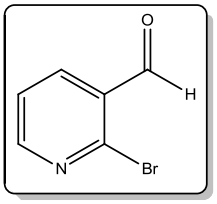
2.0, C(2)H], 10.10 [1H, s, CHO]. Spectral characteristics were consistent with previously reported data.[78]

2,6-Dichloronicotinaldehyde 70[71,77]



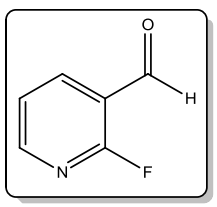
n-Butyllithium (1.6 M in hexanes, 32.5 mL, 52.0 mmol) was added dropwise to freshly distilled diisopropylamine (6.6 mL, 47.0 mmol) in freshly distilled tetrahydrofuran (60 mL) at –80 °C. Once addition was complete the reaction mixture was stirred at –80 °C for 10 min. A solution of 2,6-dichloropyridine (7.00 g, 47.00 mmol) in tetrahydrofuran (40 mL) was added dropwise to the solution and the reaction mixture was stirred for 30 min at –80 °C. Neat *N*-formylpiperidine (5.2 mL, 47.00 mmol) was added dropwise to the reaction mixture and once addition was complete, the reaction mixture was stirred for 30 min at –80 °C. The reaction was quenched by the addition of aqueous saturated ammonium chloride (30 mL). The layers were then separated and the aqueous layer extracted with ether (3 × 70 mL). The combined organic extracts were washed with brine (40 mL), dried using magnesium sulfate and concentrated under reduced pressure to give the crude *aldehyde.* Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) followed by (20:80) afforded the pure *aldehyde* **70** (4.09 g, 49%) as a white solid; m.p. 72–75 °C (lit.,[99] 74–74.5 °C); ν_{max}/cm^{-1} (KBr) 2918, 1686, 1654, 1637, 1571, 1543, 1385, 1348, 1141, 1063; δ_H (400 MHz, DMSO) 7.44 [1H, dd, *J* 8.0, 0.8, C(5)H], 8.19 [1H, d, *J* 8.4, C(4)H], 10.39 [1H, s, CHO]. Spectral characteristics were consistent with previously reported data.[71,77]

2-Bromonicotinaldehyde 71[72,74,92]



This was prepared following the procedure described for **70**, from *n*-butyllithium (1.6 M in hexanes, 34.4 mL, 50.2 mmol), freshly distilled diisopropylamine (6.8 mL, 48.49 mmol) in freshly distilled tetrahydrofuran (60 mL), a solution of 2-bromopyridine (4.2 mL, 44.30 mmol) in tetrahydrofuran (40 mL) and *N*-formylpiperidine (15.0 mL, 135 mmol) to give the crude *aldehyde.* Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) followed by (20:80) gave the purified *aldehyde* **71** (3.25 g, 40%) as a white solid; m.p. 68–70 °C (lit.,[72,92] 65 °C); ν_{max}/cm^{-1} (KBr) 3026, 2873, 1702, 1655, 1638, 1572, 1560, 1407, 1373, 1272, 1256, 1050, 832, 804; δ_H (400 MHz, $CDCl_3$) 7.44 [1H, ddd, *J* 6.9, 4.7, 0.7, C(5)H], 8.17 [1H, dd, *J* 7.5, 2.8, C(4)H], 8.58 [1H, dd, *J* 4.7, 2.4, C(6)H], 10.35 [1H, s, CHO]. Spectral properties were consistent with previously reported data.[72,74,92]

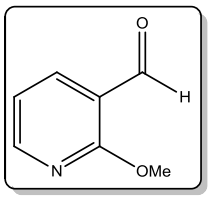
2-Fluoronicotinaldehyde 72[72,75-77]



This was prepared following the procedure described for **70**, from *n*-butyllithium (1.6 M in hexanes, 38.8 mL, 56.64 mmol), freshly distilled diisopropylamine (7.9 mL, 56.64 mmol) in freshly distilled tetrahydrofuran (60 mL), a solution of 2-fluoropyridine (4.4 mL, 51.50 mmol) in tetrahydrofuran (40 mL) and *N*-formylpiperidine (5.7 mL, 51.50 mmol) to give the crude *aldehyde.* Purification by flash chromatography on silica

gel, eluted with ethyl acetate/hexane (10:90) followed by (20:80) gave the pure *aldehyde* **72** (3.08 g, 49%) as a yellow oil; ν_{max}/cm^{-1} (film) 3070, 2884, 1705, 1670, 1601, 1575, 1464, 1435, 1396, 1295, 1273, 1245, 1176, 1097, 866, 805, 754, 632; δ_H (300 MHz, $CDCl_3$) 7.40 [1H, dddd, *J* 7.4, 4.9, 1.7, 0.8, C(5)H], 8.33 [1H, ddd, *J* 9.5, 7.5, 2.1, C(4)H], 8.49 [1H, ddd, *J* 4.8, 2.1, 1.1, C(6)H], 10.33 [1H, s, CHO]. Spectral characteristics were consistent with previously reported data.[72,76,77]

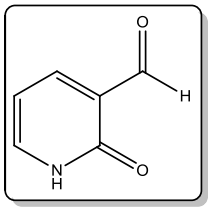
2-Methoxynicotinaldehyde 73[96]



A mixture of 2-chloronicotinaldehyde **68** (3.89 g, 22.08 mmol) and sodium methoxide (3.58 g, 66.23 mmol) in methanol (30 ml) was heated under reflux for 5 h. The solvent was evaporated and the residue was washed with water (20 mL). The mixture was extracted with ether (3 × 50 mL) and concentrated under reduced pressure to afford the crude *aldehyde* **73** as a bright yellow oil (2.68 g, 88%); ν_{max}/cm^{-1} (film) 2955, 1691, 1588, 1471, 1416, 1386, 1302, 1259, 1014; δ_H (300 MHz, $CDCl_3$) 4.08 [3H, s, OCH_3], 7.02 [1H, dd, *J* 7.5, 4.8, C(5)H], 8.12 [1H, dd, *J* 7.5, 2.1, C(4)H], 8.39 [1H, dd, *J* 5.1, 2.1, C(6)H], 10.38 [1H, s, CHO]. Spectral properties were consistent with previously reported data.[96]

2-Oxo-1,2-dihydropyridine-3-carbaldehyde 74[96,101]

Method A: Thermal conditions[96]



2-Chloronicotinaldehyde **68** (4.62 g, 26.3 mmol), aqueous hydrochloric acid (3.2 M, 20 mL) and hydrogen peroxide (30%, four drops) were added together in a round-bottom flask and the suspension was heated under reflux for 2 h, followed by cooling to room temperature. Neutralisation with saturated aqueous potassium carbonate (30 mL) induced precipitation and the solid was isolated by suction filtration to yield the crude product as a yellow solid. Extraction of the remaining neutralised solution with ethyl acetate (3 × 60 mL) followed by evaporation of solvent gave a yellow solid which was added to the above filtered portion to give the crude *aldehyde* **74** as a yellow solid (2.50 g, 77%); m.p. 220 °C (lit.,[96] 224 °C); ν_{max}/cm^{-1} (KBr) 3436, 3082, 1672 (C=O aldehyde), 1638 (C=O pyridone), 1587, 1548, 1469, 1226, 1154, 1078, 1048, 890, 787, 769; δ_H (300 MHz, DMSO-d_6) 6.38 [1H, dd, *J* 6.9, 6.9, C(5)H], 7.84 [1H, br d, *J* 4.2, C(4)H or C(6)H]*, 7.96 [1H, dd, *J* 6.9, 2.1, C(4)H or C(6)H]*, 10.05 [1H, s, CHO]. Spectral characteristics were consistent with previously reported data.[96]

* Queguiner *et al.* have assigned the signals for C(4)H and C(6)H previously,[96] however, the corresponding signals are not distinguished in this work

Method B: *Microwave conditions*[101]

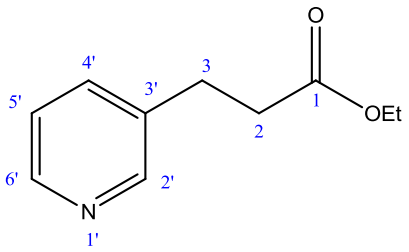
Note: The microwave reactions were carried out in a sealed tube with stirring, with an initial power input of 200 W. On reaching the desired temperature, the power decreases automatically to maintain the set temperature.

2-Chloronicotinaldehyde **68** (1.00 g, 7.06 mmol), deionised water (8 mL), hydrogen peroxide (30%, 3 drops) and aqueous hydrochloric acid (3.2 M, 3 drops) were placed in a 10 mL microwave reaction vessel, stirred and heated for 15 min at 200W at 170 °C. The dark yellow solution obtained was evaporated to afford the crude *pyridone aldehyde* **74** as a pale brown

solid (0.54 g, 62%)*; ν_{max}/cm^{-1} (KBr) 3422, 3082, 1672 (C=O aldehyde), 1637 (C=O pyridone), 1586, 1548, 1467, 1226, 1155, 1078, 1048, 890, 786, 769; δ_H (400 MHz, DMSO-d_6) 6.38 [1H, dd, *J* 6.8, 6.8, C(5)H], 7.81 [1H, dd, *J* 6.0, 2.0, C(4)H or C(6)H], 7.98 [1H, dd, *J* 6.8, 2.0, C(4)H or C(6)H]. Spectral properties were consistent with previously reported data.[101]

* The reaction was carried out four times on the above scale with all products added together to give the final sample used in the subsequent reaction.

Synthesis of esters



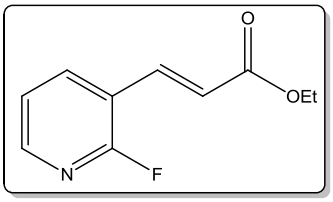
General numbering scheme for esters

The structural assignment of the α,β-unsaturated esters follows that described in the literature for analogous compounds. The assignment of the saturated esters is aided by 2D NMR HSQC and HMBC experiments on 3-(pyridine-3-yl)propanoic acid **47** (*Appendix V*) and by comparison with predicted ^{1}H and ^{13}C NMR signals for **47** described by Griffiths.[50]

Preparation of unsaturated esters

(*E*)-Ethyl 3-(2-fluoropyridin-3-yl)acrylate 79

Method A: Sodium hydride as base[41]



This procedure is based on a method described by Kato and co-workers in the preparation of **75**.[41] A suspension of sodium hydride (0.91 g, 60% mineral dispersion, 37.89 mmol) in tetrahydrofuran (60 mL) was cooled to 5 °C and neat triethyl phosphonoacetate (4.7 mL, 37.89 mmol) was added dropwise. The reaction mixture was stirred at 5 °C for 30 min followed by stirring at 1 °C for 30 min. The reaction mixture was warmed to 5 °C and a solution of 2-fluoronicotinaldehyde **72** (3.08 g, 25.26 mmol) in tetrahydrofuran (40 mL) was added dropwise. Once addition was complete, a sticky brown residue was observed at the bottom of the round-bottomed flask preventing the reaction mixture from stirring. The reaction mixture was heated under reflux for 2.5 h, allowed to cool to room temperature and quenched by addition of aqueous saturated ammonium chloride (30 mL). The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether (TBME) (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate and concentrated under reduced pressure to furnish the crude *ester* as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *ester* **79** (2.49 g, 50%) as a white solid; m.p. 46–48 °C; ν_{max}/cm^{-1} (KBr) 2984,

1720, 1706, 1639, 1442, 1320, 1188, 810; δ_H (300 MHz, DMSO-d_6) 1.27 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.22 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.79 [1H, d, *J* 16.2, C(2)<u>H</u>], 7.45 [1H, ddd, *J* 7.5, 4.8, 1.8, C(5')<u>H</u>], 7.63 [1H, d, *J* 16.2, C(3)<u>H</u>], 8.29 [1H, ddd, *J* 4.8, 1.8, 1.2, C(6')<u>H</u>], 8.45 [1H, ddd, *J* 9.6, 7.5, 1.8, C(4')<u>H</u>]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH_3, $CH_2\underline{C}H_3$], 60.4 [CH_2, $\underline{C}H_2CH_3$], 116.7 [C, d, $^2J_{CF}$ 26.4, <u>C</u>(3')], 122.6 [2 × CH, 2 × overlapping d, $^4J_{CF}$ < 4.0, <u>C</u>(2)H and <u>C</u>(5')H]*, 135.0 [CH, d, $^3J_{CF}$ 2.3, <u>C</u>(3)H], 140.3 [CH, d, $^3J_{CF}$ 3.4, <u>C</u>(4')H], 148.9 [CH, d, $^3J_{CF}$ 15.1, <u>C</u>(6')H], 160.4 [C, d, $^1J_{CF}$ 241.4, <u>C</u>(2')F], 165.5 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}FNO_2$ $[M+H]^+$, 196.0774. Found 196.0766. m/z (ES+) 237.1 (100%), 196.0 $[(M+H)^+$, 76%].

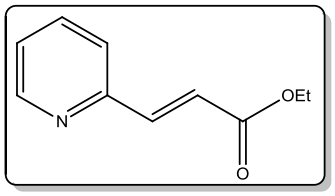
* Interpretation of the J_{CF} values for signal at δ_C 122.6 ppm is assuming the overlapping doublets correspond to the two adjacent doublets, $^4J_{CF}$ 1.9, 2.6 Hz but this may not be correct.

Method B: Lithium chloride/DBU as base[35]

Lithium chloride (1.23 g, 28.92 mmol) was dissolved in distilled acetonitrile (70 mL) and the solution was cooled to 0 °C. A solution of triethyl phosphonoacetate (3.6 mL, 26.29 mmol) in acetonitrile (20 mL) was added dropwise. A solution of aldehyde **72** (3.21 g, 26.29 mmol) in acetonitrile (30 mL) was subsequently added dropwise to the reaction mixture. After stirring for 5 min, neat 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.9 mL, 26.29 mmol) was added dropwise still stirring at 0 °C and then the reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether (70 ml), washed with aqueous saturated ammonium chloride (30 mL), brine (30 mL), dried using magnesium sulfate, filtered through a pad of Celite® and concentrated under reduced pressure to provide the crude ester as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) afforded the *ester* **79** (2.53 g, 49%) as a yellow crystalline solid; ν_{max}/cm^{-1} (KBr) 2984, 1712, 1641, 1434, 1408, 1311, 1281, 1320, 1179; δ_H (300 MHz, $CDCl_3$)* 1.35 [3H, t, *J* 6.9, $CH_2C\underline{H}_3$], 4.29 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.60 [1H, d, *J* 16.2, C(2)<u>H</u>], 7.25 [1H, ddd, *J* 6.9, 4.8, 2.1, C(5')<u>H</u>]**, 7.71 [1H, d, *J* 16.2, C(3)<u>H</u>], 7.94 [1H, ddd, *J* 9.3, 8.1, 2.1, C(4')<u>H</u>]***, 8.22 [1H, dt, *J* 4.8, 1.8, C(6')<u>H</u>]***.

* Sample contains ~16 mol% *cis* isomer. Signals for the *cis* isomer in ^{1}H NMR spectrum are overlapping signals δ_H ~1.35 and 4.29 ppm with the *trans* isomer and distinctive signals at 6.34 [0.2H, d, *J* 15.9, C(2)<u>H</u>], 6.82 [0.2H, dd, *J* 7.5, 4.8], 7.79 [0.2H, d, *J* 15.9, C(3)<u>H</u>].
** Integration is higher than expected due to overlap with $CDCl_3$.
*** From ^{1}H NMR using $CDCl_3$, it appears that signals for C(4')<u>H</u> and C(6')<u>H</u> have swapped positions with respect to ^{1}H NMR analysis using DMSO-d_6 in method A above.

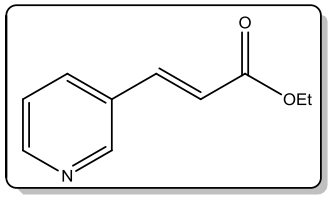
(*E*)-Ethyl 3-(pyridin-2-yl)acrylate 40[37]



This was prepared following the procedure described for **79** (Method B: Lithium chloride/DBU as base), from lithium chloride (3.05 g, 71.89 mmol) dissolved in acetonitrile (100 mL), triethyl phosphonoacetate (8.2 mL, 65.4 mmol) in acetonitrile (50 mL), a solution of 2-pyridine carboxaldehyde (5.6 mL, 65.4 mmol) in acetonitrile (20 mL) and DBU (9.8 mL, 65.4 mmol) gave the crude *ester* as a crystalline orange solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (15:85) and gradually increased to (20:80) afforded the pure *ester* **40** (6.62 g, 57%) as a colourless oil which later solidified to provide a white solid; ν_{max}/cm^{-1} (film) 2983, 1715, 1646, 1583, 1567, 1469, 1433, 1368, 1319, 1262, 1205, 1163, 1035, 982, 787, 746; δ_H (400 MHz, $CDCl_3$) 1.33 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.28 [2H, q, *J*

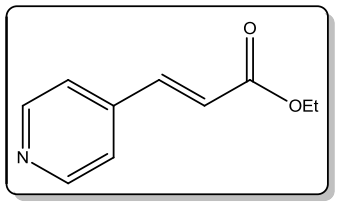
7.2, C<u>H</u>$_2$CH$_3$], 6.92 [1H, d, *J* 15.6, C(2)<u>H</u>], 7.26 [1H, ddd, *J* 6.8, 4.8, 0.8, C(5')<u>H</u>], 7.43 [1H, d, *J* 8.0, C(3')<u>H</u>], 7.68 [1H, d, *J* 16.0, C(3)<u>H</u>], 7.70 [1H, ddd, *J* 9.6, 8.0, 2.0, C(4')<u>H</u>], 8.64 [1H, d with further unresolved splitting, *J* 4.0, C(6')<u>H</u>]. Spectral properties were consistent with reported data,[37] although **40** was not prepared previously using this method.

(*E*)-Ethyl 3-(pyridin-3-yl)acrylate 41[37,38]



This was prepared following the procedure described for **79** (Method B: Lithium chloride/DBU as base), from lithium chloride (4.35 g, 103 mmol) dissolved in acetonitrile (100 mL), triethyl phosphonoacetate (11.7 mL, 93.36 mmol) in acetonitrile (50 ml), a solution of 3-pyridine carboxaldehyde (8.8 mL, 93.36 mmol) in acetonitrile (20 mL) and DBU (14.0 mL, 93.36 mmol) to furnish the crude *ester* as a crystalline orange solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (15:85) and gradually increased to (20:80) gave the pure *ester* **41** (8.81 g, 53%) as a colourless oil which later solidified to give a white solid; m.p. 154–155 °C (lit.,[38] 156–158 °C); ν_{max}/cm^{-1} (film) 2983, 1714, 1643, 1588, 1570, 1478, 1417, 1368, 1314, 1267, 1220, 1188, 1044, 1026, 983, 807, 699; δ_H (400 MHz, $CDCl_3$) 1.35 [3H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$], 4.29 [2H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$], 6.52 [1H, d, *J* 15.9, C(2)<u>H</u>], 7.34 [1H, dd, *J* 7.8, 4.8, C(5')<u>H</u>], 7.68 [1H, d, *J* 16.2, C(3)<u>H</u>], 7.85 [1H, dt, *J* 7.8, 1.8, C(4')<u>H</u>], 8.61 [1H, dd, *J* 4.8, 1.8, C(6')<u>H</u>], 8.72 [1H, d, *J* 1.8, C(2')<u>H</u>]. Spectral characteristics were consistent with reported data,[37] although **41** was not previously prepared using this method.

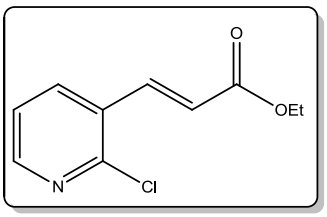
(*E*)-Ethyl 3-(pyridin-4-yl)acrylate 42[36,40,282]



This was prepared following the procedure described for **79** (Method B: Lithium chloride/DBU as base), from lithium chloride (2.18 g, 51.35 mmol) dissolved in acetonitrile (100 mL), triethyl phosphonoacetate (5.8 mL, 46.7 mmol) in acetonitrile (50 mL), a solution of 4-pyridine carboxaldehyde (4.5 mL, 46.7 mmol) in acetonitrile (20 mL) and DBU (7.0 mL, 46.7 mmol) to give the crude *ester* as a crystalline orange solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) furnished the pure *ester* **42** (4.40 g, 53%) as a fluffy white solid; m.p. 64 °C (lit.,[40] 64–66 °C); ν_{max}/cm^{-1} (KBr) 2983, 1709, 1642, 1599, 1548, 1421, 1365, 1327, 1301, 1189, 1035; δ_H (400 MHz, $CDCl_3$) 1.35 [3H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$], 4.29 [2H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$], 6.59 [1H, d, *J* 16.0, C(2)<u>H</u>], 7.36 [2H, d, *J* 6.0, C(3')<u>H</u> and C(5')<u>H</u>], 7.59 [1H, d, *J* 16.0, C(3)<u>H</u>], 8.65 [2H, d, *J* 5.6, C(2')<u>H</u> and C(6')<u>H</u>]. Spectral properties were consistent with reported data,[282] although **42** was not previously prepared using this method.

(*E*)-Ethyl 3-(2-chloropyridin-3-yl)acrylate 75[41,70]

Method A: Sodium hydride as base



This was prepared following the procedure described for **79** (Method A: Sodium hydride as base), from a suspension of sodium hydride (1.57 g, 60% mineral dispersion, 65.47 mmol) in freshly distilled tetrahydrofuran (60 mL), neat triethyl

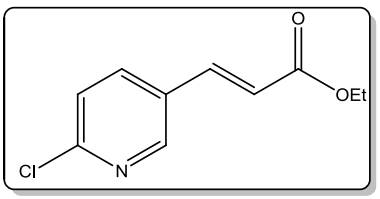
phosphonoacetate (13.0 mL, 65.47 mmol) and a solution of 2-chloronicotinaldehyde **68** (6.18 g, 43.65 mmol) in tetrahydrofuran (40 mL) to give the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) yielded the purified *ester* **75** (9.04 g, 98%)* as a white solid; m.p. 48–50 °C (lit.,[70] 49.1–49.8 °C); ν_{max}/cm^{-1} (KBr) 2982, 1712, 1636, 1577, 1557, 1403, 1313, 1271, 1185, 1067, 804; δ_H (400 MHz, DMSO-d_6) 1.35 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.30 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.45 [1H, d, *J* 16.4, C(2)H], 7.45 [1H, dd, *J* 8.0, 4.8, C(5')H], 7.82 [1H, d, *J* 16.0, C(3)H], 8.42 [1H, d, *J* 7.6, C(4')H], 8.47 [1H, dd, *J* 4.8, 2.0, C(6')H]. Infrared properties were consistent with previously reported data,[70] while ^{1}H NMR spectroscopy was previously carried out using $CDCl_3$ as solvent.[41,70]

* Sample contains ~15% starting aldehyde.

Method B: Lithium chloride/DBU as base

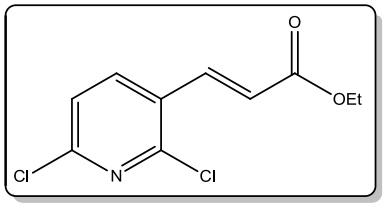
This was prepared following the procedure described for **79** (Method B: Lithium chloride/DBU as base), from lithium chloride (2.29 g, 54.09 mmol) dissolved in distilled acetonitrile (70 mL), triethyl phosphonoacetate (6.2 mL, 49.17 mmol) in acetonitrile (20 mL), a solution of aldehyde **68** (6.96 g, 49.17 mmol) in acetonitrile (20 mL) and DBU (7.4 mL, 49.17 mmol) to afford the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) furnished the pure *ester* **75** (5.78 g, 56%) as a yellow crystalline solid; ν_{max}/cm^{-1} (KBr) 1718, 1638, 1578, 1560, 1402, 1314, 1274, 1183, 1070; δ_H (400 MHz, $CDCl_3$) 1.35 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.30 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.45 [1H, d, *J* 16.4, C(2)H], 7.29 [1H, dd, *J* 8.0, 4.8, C(5')H], 7.91 [1H, dd, *J* 8.0, 1.6, C(4')H], 7.98 [1H, d, *J* 16.0, C(3)H], 8.40 [1H, dd, *J* 4.8, 2.0, C(6')H]. Spectral properties were consistent with previously reported data.[41,70]

(*E*)-Ethyl 3-(6-chloropyridin-3-yl)acrylate 76[104,105]



This was prepared following the procedure described for **79** (Method A: Sodium hydride as base), from sodium hydride (1.20 g, 60% mineral dispersion, 50.31 mmol) in freshly distilled tetrahydrofuran (60 mL), neat triethyl phosphonoacetate (10.0 ml, 50.31 mmol) and a solution of 6-chloronicotinaldehyde **69** (4.75 g, 33.54 mmol) in tetrahydrofuran (40 mL) to yield the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *ester* **76** (3.95 g, 56%) as a white solid; m.p. 79–81 °C (lit.,[105] 81 °C); ν_{max}/cm^{-1} (KBr) 2984, 1717, 1703, 1644, 1582, 1559, 1468, 1320, 1306, 1175, 984, 831; δ_H (400 MHz, $CDCl_3$) 1.35 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.28 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.48 [1H, d, *J* 16.0 , C(2)H], 7.36 [1H, d, *J* 8.4, C(5')H], 7.63 [1H, d, *J* 16.0, C(3)H], 7.80 [1H, dd, *J* 8.4, 2.4, C(4')H], 8.51 [1H, d, *J* 2.4, C(2')H]. Spectral properties were consistent with previously reported data.[105]

(*E*)-Ethyl 3-(2,6-dichloropyridin-3-yl)acrylate 77

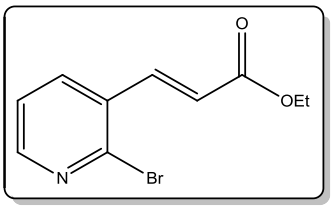


This was prepared following the procedure described for **79** (Method A: Sodium hydride as base), from a suspension of sodium hydride (0.80 g, 60% mineral dispersion, 33.17 mmol) in tetrahydrofuran (60 mL), neat triethyl phosphonoacetate (6.6 mL, 33.17 mmol) and a solution of

2,6-dichloropyridinecarboxaldehyde **70** (3.89 g, 22.14 mmol) in tetrahydrofuran (40 mL) to afford the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) afforded the pure *ester* **77** (2.00 g, 37%) as a white solid; m.p. 46–48 °C; ν_{max}/cm^{-1} (KBr) 2991, 1737, 1712, 1636, 1570, 1544, 1425, 1317, 1152, 975; δ_H (300 MHz, DMSO-d_6) 1.26 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.22 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.86 [1H, d, *J* 16.0, C(2)<u>H</u>], 7.66 [1H, d with further unresolved splitting, *J* 8.4, C(5')<u>H</u>], 7.73 [1H, d, *J* 16.0, C(3)<u>H</u>], 8.46 [1H, d, *J* 8.4, C(4')<u>H</u>]; δ_C (75.5 MHz, DMSO-d_6) 14.1 [CH_3, $CH_2\underline{C}H_3$], 60.6 [CH_2, $\underline{C}H_2CH_3$], 123.9 [CH, <u>C</u>(2)H or <u>C</u>(5')H], 124.3 [CH, <u>C</u>(2)H or <u>C</u>(5')H], 128.0 [C, <u>C</u>(3')], 136.6 [CH, <u>C</u>(4')H or <u>C</u>(3)H], 140.1 [CH, <u>C</u>(4')H or <u>C</u>(3)H], 148.8 [C, <u>C</u>(2')Cl or <u>C</u>(6')Cl], 149.9 [C, <u>C</u>(2')Cl or <u>C</u>(6')Cl], 165.3 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{10}{}^{37}Cl^{35}ClNO_2$ $[M+H]^+$, 248.0059. Found 248.0056 and exact mass calculated for $C_{10}H_{10}{}^{35}Cl_2NO_2$ $[M+H]^+$, 246.0089. Found 246.0082. m/z (ES+) 248.0 {$[(C_{10}H_{10}{}^{37}Cl^{35}ClNO_2)^+]$, 64%} 246.0 {$[(C_{10}H_{10}{}^{35}Cl_2NO_2)^+]$, 100%}, 104.9 (22%).

(*E*)-Ethyl 3-(2-bromopyridin-3-yl)acrylate 78

Method A: Sodium hydride as base



This was prepared following the procedure described for **79** (Method A: Sodium hydide as base), from sodium hydride (0.63 g, 60% mineral dispersion, 26.22 mmol) in freshly distilled tetrahydrofuran (60 mL), neat triethyl phosphonoacetate (3.3 mL, 26.22 mmol) and a solution of 2-bromonicotinaldehyde **71** (3.25 g, 17.48 mmol) in tetrahydrofuran (40 mL) to furnish the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) afforded the pure *ester* **78** (1.50 g, 34%) as a colourless oil which readily solidified to give a white solid; m.p. 56–58 °C; ν_{max}/cm^{-1} (KBr) 2982, 1715, 1638, 1573, 1553, 1448, 1397, 1300, 1271, 1185, 1052, 975, 803; δ_H (300 MHz, DMSO-d_6) 1.26 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.21 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.75 [1H, d, *J* 15.9, C(2)<u>H</u>], 7.50 [1H, dd, *J* 7.2, 4.5, C(5')<u>H</u>], 7.74 [1H, d, *J* 15.9, C(3)<u>H</u>], 8.31 [1H, dd, *J* 7.8, 1.8, C(4')<u>H</u>], 8.39 [1H, dd, *J* 4.5, 1.8, C(6')<u>H</u>]; δ_C (75.5 MHz, DMSO-d_6) 14.0 [CH_3, $CH_2\underline{C}H_3$], 60.5 [CH_2, $\underline{C}H_2CH_3$], 123.2 [CH, <u>C</u>(2)H or <u>C</u>(5')H], 123.9 [CH, <u>C</u>(2)H or <u>C</u>(5')H], 130.9 [C, <u>C</u>(3')], 136.8 [CH, <u>C</u>(4')H or <u>C</u>(3)H], 140.0 [CH, <u>C</u>(4')H or <u>C</u>(3)H], 143.4 [C, <u>C</u>(2')Br], 151.3 [CH, <u>C</u>(6')H], 165.3 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{79}BrNO_2$ $[M+H]^+$, 255.9973. Found 255.9978. m/z (ES+) 299.0 (78%), 297.0 (76%), 258.0 {$[(C_{10}H_{11}{}^{81}BrNO_2)^+]$, 56%}, 256.0 {$[(C_{10}H_{11}{}^{79}BrNO_2)^+]$, 100%}, 235.0 (12%).

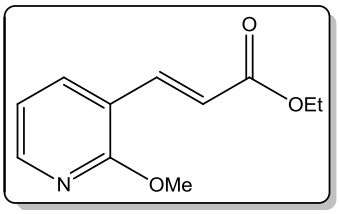
Method B: Lithium chloride/DBU as base

This was prepared following the procedure described for **79** (Method B: Lithium chloride /DBU as base), from lithium chloride (0.69 g, 16.33 mmol) dissolved in doubly distilled acetonitrile (70 mL), triethyl phosphonoacetate (1.9 mL, 14.85 mmol) dissolved in acetonitrile (20 mL) followed by a solution of 2-bromonicotinaldehyde **71** (2.76 g, 14.85 mmol) in acetonitrile (10 mL) and DBU (2.2 mL, 14.85 mmol) to generate the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) afforded the *ester* **78** (2.77 g, 73%)* as a colourless oil which readily solidified to give a white solid; ν_{max}/cm^{-1} (KBr) 2982, 1715, 1638, 1573, 1553, 1397, 1312, 1270, 1184, 1052, 974, 803; δ_H (400 MHz, $CDCl_3$) 1.36 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.30 [2H, q, *J* 7.2,

C<u>H</u>$_2$CH$_3$], 6.42 [1H, d, *J* 16.0, C(2)<u>H</u>], 7.32 [1H, dd, *J* 8.0, 4.8, C(5')<u>H</u>], 7.87 [1H, dd, *J* 8.0, 2.0, C(4')<u>H</u>], 7.94 [1H, d, *J* 16.0, C(3)<u>H</u>], 8.37 [1H, dd, *J* 4.8, 2.0, C(6')<u>H</u>].

* Sample contains ~8 mol% aldehyde **71** as well as 3 mol% of the *cis* isomer. The signals ascribed to the *cis* isomer are δ_H 6.15 ppm [0.03H, *J* 12.0] and δ_H 7.13 ppm [0.03H, *J* 12.0].

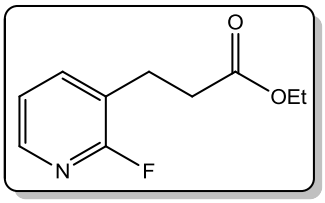
(*E*)-Ethyl 3-(2-methoxypyridin-3-yl)acrylate 80



This was prepared following the procedure described for **79** (Method A: Sodium hydride as base), from a suspension of sodium hydride (0.70 g, 60% mineral dispersion, 29.27 mmol) in tetrahydrofuran (60 mL), neat triethyl phosphonoacetate (5.8 mL, 29.27 mmol) and a solution of 2-methoxynicotinaldehyde **73** (2.68 g, 19.52 mmol) in tetrahydrofuran (40 mL) to give the crude *ester*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) the pure *ester* **80** (2.18 g, 54%) as a colourless oil which solidified after storage at 5 °C overnight; m.p. 48–50 °C; ν_{max}/cm^{-1} (film) 2983, 2953, 1712, 1635, 1587, 1574, 1467, 1409, 1312, 1280, 1177, 1018, 987, 798, 775; δ_H (400 MHz, $CDCl_3$) 1.34 [3H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$], 4.03 [3H, s, OC<u>H</u>$_3$], 4.27 [2H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$], 6.61 [1H, d, *J* 15.9, C(2)<u>H</u>], 6.91 [1H, dd, *J* 7.2, 4.8, C(5')<u>H</u>], 7.73 [1H, dd, *J* 7.5, 2.1, C(4')<u>H</u>], 7.80 [1H, d, *J* 16.2, C(3)<u>H</u>], 8.16 [1H, dd, *J* 4.8, 1.8, C(6')<u>H</u>]; δ_C (75.5 MHz, $CDCl_3$) 14.3 [CH$_3$, CH$_2$<u>C</u>H$_3$], 53.6 [CH$_3$, O<u>C</u>H$_3$], 60.4 [CH$_2$, <u>C</u>H$_2$CH$_3$], 116.9 [CH, <u>C</u>(5')H], 117.9 [C, <u>C</u>(3')], 120.6 [CH, <u>C</u>(2)H], 137.7 [CH, <u>C</u>(3)H or <u>C</u>(4')H], 138.8 [CH, <u>C</u>(3)H or <u>C</u>(4')H], 148.1 [CH, <u>C</u>(6')H], 161.9 [C, <u>C</u>(2')OCH$_3$], 167.0 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact mass calculated for $C_{11}H_{14}NO_3$ [M+H]$^+$, 208.0974. Found 208.0971. m/z (ES+) 209.3 (18%), 208.3 [(M+H)$^+$, 100%].

Synthesis of saturated esters

Ethyl 3-(2-fluoropyridin-3-yl)propanoate 99

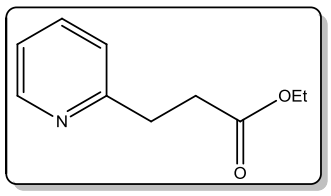


A mixture of (*E*)-ethyl 3-(2-fluoropyridin-3-yl)acrylate **79** (2.48 g, 12.70 mmol) and palladium on carbon (10%, 0.25 g) in distilled ethyl acetate (70 mL) was shaken under hydrogen at 50 psi, for 30 h at room temperature. The reaction progress was monitored by TLC analysis and ^{1}H NMR spectroscopy of a small portion of the sample. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet.* Concentration of the filtrate under reduced pressure gave the crude *ester* **99** (2.31 g, 92%) as a dark orange oil; ν_{max}/cm^{-1} (film) 2983, 2936, 1735, 1608, 1579, 1439, 1376, 1245, 1182, 1105; δ_H (300 MHz, $CDCl_3$) 1.20 [3H, t, *J* 7.2, CH$_2$C<u>H</u>$_3$], 2.62 [2H, t, *J* 7.5, C(2)<u>H</u>$_2$], 2.94 [1H, t, *J* 7.5, C(3)<u>H</u>$_2$], 4.09 [2H, q, *J* 7.2, C<u>H</u>$_2$CH$_3$], 7.09 [1H, ddd, *J* 7.5, 4.8, 1.8, C(5')<u>H</u>], 7.64 [1H, ddd, *J* 9.6, 7.5, 2.1, C(4')<u>H</u>], 8.06 [1H, br d with further unresolved splitting, *J* 4.8, C(6')<u>H</u>]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH$_3$, CH$_2$<u>C</u>H$_3$], 24.4 [CH$_2$, <u>C</u>(3)H$_2$], 33.5 [CH$_2$, <u>C</u>(2)H$_2$], 60.6 [CH$_2$, <u>C</u>H$_2$CH$_3$], 121.4 [CH, d, $^4J_{CF}$ 4.1, <u>C</u>(5')H], 122.2 [C, d, $^2J_{CF}$ 30.7, <u>C</u>(3')], 141.1 [CH, d, $^3J_{CF}$ 5.7, <u>C</u>(4')H], 145.5 [CH, d, $^3J_{CF}$ 14.7, <u>C</u>(6')H], 161.9 [C, d, $^1J_{CF}$ 238.8, <u>C</u>(2')F], 172.2 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact

mass calculated for $C_{10}H_{13}FNO_2$ $[M+H]^+$, 198.0930. Found 198.0909. m/z (ES+) 264.1 (18%), 263.2 (100%), 239.0 (6%), 198.1 $[(M+H)^+$, 14%], 180.1 (10%).

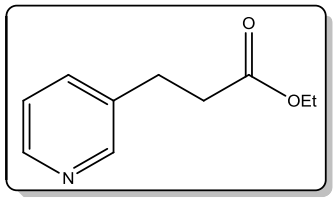
* It is important to keep the catalyst wet with solvent while filtering the product as palladium on carbon is a pyrophoric catalyst.

Ethyl 3-(pyridin-2-yl)propanoate 43[36,43]



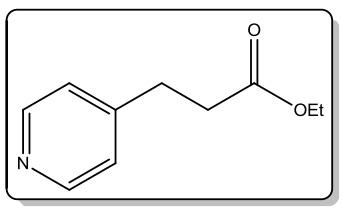
This was prepared following the procedure described for **99**, from (*E*)-ethyl 3-(pyridin-2-yl)acrylate **40** (6.62 g, 37.36 mmol) and palladium on carbon (5%, 0.66 g) in undistilled ethanol (70 mL), under hydrogen at 60 psi, for 24 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure gave the crude *ester* **43** (5.05 g, 75%) as a colourless oil; ν_{max}/cm^{-1} (film) 2983, 2935, 1733, 1594, 1570, 1476, 1437, 1374, 1180, 1097, 1041, 755; δ_H (400 MHz, $CDCl_3$) 1.22 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.79 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 3.11 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 4.12 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.11 [1H, dd, *J* 7.6, 4.8, C(5')$\underline{H}$], 7.19 [1H, d, *J* 7.8, C(3')$\underline{H}$], 7.58 [1H, ddd, *J* 7.6, 7.6, 1.6, C(4')$\underline{H}$], 8.51 [1H, br d with further unresolved splitting, *J* 4.9, C(6')$\underline{H}$]. Spectral properties were consistent with previously reported data.[43]

Ethyl 3-(pyridin-3-yl)propanoate 44[42,283]



This was prepared following the procedure described for **99**, from (*E*)-ethyl 3-(pyridin-3-yl)acrylate **41** (8.81 g, 49.70) and palladium on carbon (5%, 0.88 g) in undistilled ethanol (70 mL), under hydrogen at 60 psi, for 24 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure furnished the crude *ester* **44** (8.49 g, 95%) as a colourless oil; ν_{max}/cm^{-1} (film) 2983, 1732, 1594, 1577, 1480, 1426, 1375, 1187, 1040, 1030, 715; δ_H (400 MHz, $CDCl_3$) 1.19 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.60 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 2.92 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 4.09 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.18 [1H, dd, *J* 7.2, 4.8, C(5')$\underline{H}$], 7.50 [1H, dt, *J* 8.0, 1.6, C(4')$\underline{H}$], 8.38–8.47 [2H, m contains dd at 8.41, *J* 4.8, 1.2, C(6')$\underline{H}$ and d at 8.44, *J* 4.8, C(2')$\underline{H}$]. Spectral characteristics were consistent with previously reported data.[42]

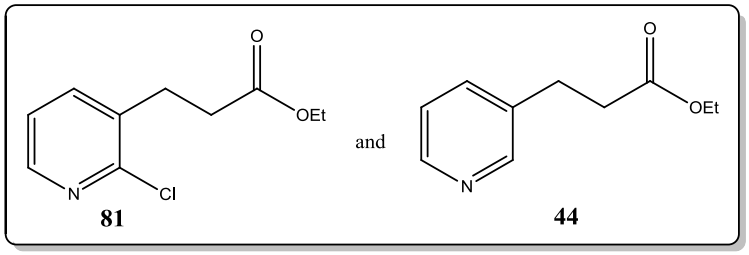
Ethyl 3-(pyridin-4-yl)propanoate 45[36,44]



This was prepared following the procedure described for **99**, from (*E*)-ethyl 3-(pyridin-4-yl)acrylate **42** (4.40 g, 24.8 mmol) and palladium on carbon (5%, 0.44 g) in undistilled ethanol (70 mL), under hydrogen at 60 psi, for 24 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the

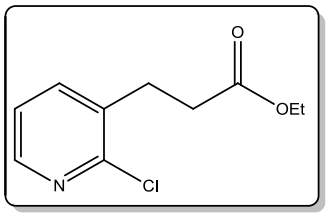
filtrate under reduced pressure yielded the crude *ester* **45** (4.06 g, 91%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2983, 1734, 1603, 1560, 1417, 1375, 1186, 1039, 812; δ_H (400 MHz, $CDCl_3$) 1.23 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.64 [2H, t, *J* 7.2, C(2)$\underline{H}_2$], 2.95 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 4.13 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.14 [2H, dd, *J* 4.4, 1.6, C(3')$\underline{H}$ and C(5')$\underline{H}$], 8.46 [2H, dd, *J* 4.4, 1.6, C(2')$\underline{H}$ and C(6')$\underline{H}$]. Spectral properties were consistent with previously reported data.[44]

Attempted hydrogenation of (*E*)-Ethyl 3-(2-chloropyridin-3-yl)acrylate 75



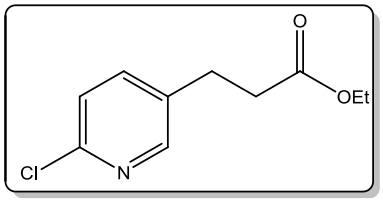
Hydrogenation was attempted following the procedure described for **99**, from ester **75** (2.87 g, 13.55 mmol) and palladium on carbon (5%, 0.29 g) in distilled ethyl acetate (70 mL), under hydrogen at 60 psi, for 48 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute it, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure yielded the crude mixture. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) furnished the pure *ester* **81** (0.89 g, 31%) as a pale yellow solid followed by the more polar *dehalogenated ester* **44** (0.40 g, 14%) as a pale orange oil. Spectral properties for esters **81** and **44** were consistent with spectral data obtained elsewhere in this work.

Ethyl 3-(2-chloropyridin-3-yl)propanoate 81[112]



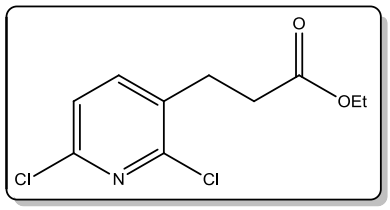
Copper(I) chloride (4.23 g, 42.73 mmol) and $NaBH_4$ (0.81 g, 42.73 mmol) were sequentially added to a solution of ester **75** (9.04 g, 42.73 mmol) in methanol/water (80/20 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then additional $NaBH_4$ (2 × 0.81 g, 2 × 42.73 mmol) was added in two portions over 2 h at 0 °C. The reaction was quenched by addition of aqueous saturated ammonium chloride (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate, filtered and concentrated under reduced pressure to yield the crude *saturated ester* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *saturated ester* **81** (4.10 g, 45%) as a colourless oil; ν_{max}/cm^{-1} (film) 2983, 1733, 1564, 1410, 1187, 1073, 802; δ_H (400 MHz, $CDCl_3$) 1.24 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.69 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 3.06 [2H, t, *J* 7.2, C(3)$\underline{H}_2$], 4.13 [2H, q, *J* 6.8, $C\underline{H}_2CH_3$], 7.19 [1H, dd, *J* 7.6, 4.8, C(5')$\underline{H}$], 7.63 [1H, dd, *J* 7.2 1.6, C(4')$\underline{H}$], 8.27 [1H, dd, *J* 4.4, 1.6, C(6')$\underline{H}$]. Spectral properties were consistent with previously reported data.[112]

Ethyl 3-(6-chloropyridin-3-yl)propanoate 93[113]



This was prepared following the procedure described for **81**, from a solution of ester **76** (3.95 g, 18.66 mmol) in methanol/water (80/20 mL), copper(I) chloride (1.85 g, 18.66 mmol), $NaBH_4$ (0.706 g, 18.66 mmol) and additional two equivalents of $NaBH_4$ (2 × 0.71 g, 2 × 18.66 mmol) to furnish the crude *ester* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *saturated ester* **93** (2.65 g, 66%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2983, 1733, 1587, 1566, 1461, 1387, 1374, 1190, 1106; δ_H (400 MHz, $CDCl_3$) 1.23 [3H, t, *J* 6.8, $CH_2C\underline{H}_3$], 2.63 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 2.94 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 4.13 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.25 [1H, d, *J* 8.4, C(5')$\underline{H}$], 7.53 [1H, dd, *J* 8.4, 2.4, C(4')$\underline{H}$], 8.26 [1H, d, *J* 2.4, C(2')$\underline{H}$].

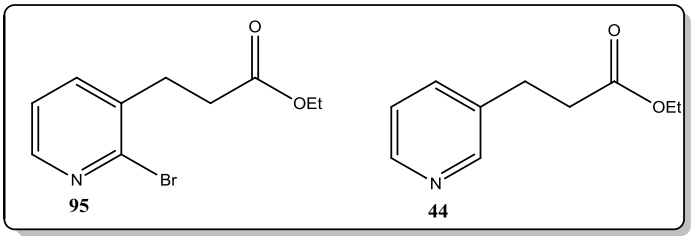
Ethyl 3-(2,6-dichloropyridin-3-yl)propanoate 94



This was prepared following the procedure described for **81**, from a solution of ester **77** (2.00 g, 8.12 mmol) in methanol/water (80/20 mL), copper(I) chloride (0.80 g, 8.12 mmol), $NaBH_4$ (0.31 g, 8.12 mmol) and additional two equivalents of $NaBH_4$ (2 × 0.31 g, 2 × 8.12 mmol) to afford the crude *ester* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *saturated ester* **94** (1.01 g, 50%) as a colourless oil; ν_{max}/cm^{-1} (film) 2982, 2939, 1731, 1579, 1551, 1428, 1365, 1191, 1143, 1073, 830; δ_H (400 MHz, $CDCl_3$) 1.24 [3H, t, *J* 6.9, $CH_2C\underline{H}_3$], 2.67 [2H, t, *J* 7.2, C(2)$\underline{H}_2$], 3.03 [2H, t, *J* 7.2, C(3)$\underline{H}_2$], 4.10 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.19 [1H, d, *J* 8.1, C(5')$\underline{H}$], 7.58 [1H, d, *J* 7.8, C(4')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH_3, $CH_2\underline{C}H_3$], 27.6 [CH_2, $\underline{C}(3)H_2$], 32.8 [CH_2, $\underline{C}(2)H_2$], 60.7 [CH_2, $\underline{C}H_2CH_3$], 123.0 [CH, $\underline{C}$(5')H], 133.4 [C, $\underline{C}$(3')], 141.6 [CH, $\underline{C}$(4')H], 148.1 [C, $\underline{C}$(2')Cl or $\underline{C}$(6')Cl], 149.9 [C, $\underline{C}$(2')Cl or $\underline{C}$(6')Cl], 172.0 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{12}{}^{37}Cl^{35}ClNO_2$ $[M+H]^+$, 250.0216. Found 250.0238 and exact mass calculated for $C_{10}H_{12}{}^{35}Cl_2NO_2$ $[M+H]^+$, 248.0245. Found 248.0236. m/z (ES+) 250.1 {$[(C_{10}H_{12}{}^{37}Cl^{35}ClNO_2)^+]$, 72%}, 248.1 {$[(C_{10}H_{12}{}^{35}Cl_2NO_2)^+]$, 100%}.

Attempted reduction of (*E*)-Ethyl 3-(2-bromopyridin-3-yl)acrylate 78

Method A: $NaBH_4$/Cu(I)Cl reduction

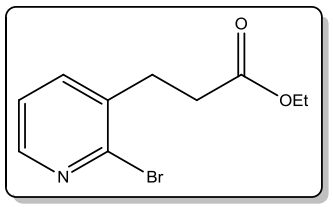


This was prepared following the procedure described for **81**, from a solution of (*E*)-ethyl 3-(2-bromopyridin-3-yl)acrylate **78** (1.50 g, 5.86 mmol) in methanol/water (80/20 mL) copper(I) chloride (0.58 g, 5.86 mmol), $NaBH_4$ (0.22 g, 5.86 mmol) and additional two equivalents of $NaBH_4$ (2 × 0.22 g, 2 × 5.86 mmol) to give the crude *ester* as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl

acetate/hexane (20:80) to (40:60) afforded the pure *saturated ester* **95** (0.16 g, 11%) as a colourless oil followed by the more polar *dehalogenated ester* **44** (0.47 g, 32%) as a pale yellow oil**.** Spectral data for **44** was consistent with data obtained elsewhere in this work. Spectral data for **95**; ν_{max}/cm^{-1} (film) 2982, 1733, 1579, 1560, 1405, 1374, 1186, 1053; δ_H (300 MHz, $CDCl_3$) 1.24 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.69 [2H, t, *J* 7.2, C(2)$\underline{H}_2$], 3.05 [2H, t, *J* 7.5, C(3)$\underline{H}_2$], 4.14 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.21 [1H, dd, *J* 7.5, 4.8, C(5')$\underline{H}$], 7.59 [1H, dd, *J* 7.5, 2.1, C(4')$\underline{H}$], 8.24 [1H, dd, *J* 4.5, 1.8, C(6')$\underline{H}$].

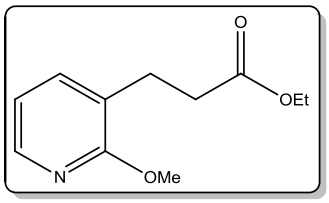
Ethyl 3-(2-bromopyridin-3-yl)propanoate 95

Method B: Hydrogenation using Wilkinson's catalyst[115]



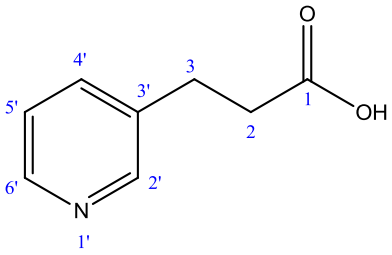
A solution of ester **78** (2.77 g, 10.80 mmol) and Wilkinson's catalyst **96** (0.50 g, 0.54 mmol) in undistilled ethanol (70 mL) was shaken under hydrogen at 50 psi, for 48 h at room temperature. The reaction progress was monitored by ^{1}H NMR spectroscopy and TLC analysis. The solvent was evaporated to afford the crude *ester* as a brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *saturated ester* **95** (2.27 g, 81%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2982, 1733, 1579, 1559, 1405, 1374, 1186, 1053; δ_H (400 MHz, $CDCl_3$) 1.23 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.68 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 3.04 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 4.12 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.20 [1H, dd, *J* 7.2, 4.4, C(5')$\underline{H}$], 7.58 [1H, dd, *J* 7.6, 1.6, C(4')$\underline{H}$], 8.22 [1H, dd, *J* 4.8, 1.6, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 14.0 [CH_3, $CH_2\underline{C}H_3$], 30.3 [CH_2, $\underline{C}$(3)H_2], 33.2 [CH_2, $\underline{C}$(2)H_2], 60.5 [CH_2, $\underline{C}H_2CH_3$], 122.8 [CH, $\underline{C}$(5')H], 137.0 [C, $\underline{C}$(2')Br or $\underline{C}$(3')], 138.6 [CH, $\underline{C}$(4')H], 144.1 [C, $\underline{C}$(2')Br or $\underline{C}$(3')], 147.9 [CH, $\underline{C}$(6')H], 172.0 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{13}{}^{79}BrNO_2$ $[M+H]^+$, 258.0130. Found 258.0140. m/z (ES+) 260.1 {[$(C_{10}H_{13}{}^{81}BrNO_2)^+$], 90%}, 258.1 {[$(C_{10}H_{13}{}^{79}BrNO_2)^+$], 100%}.

Ethyl 3-(2-methoxypyridin-3-yl)propanoate 100[284]



This was prepared following the procedure described for **99**, from (*E*)-ethyl 3-(2-methoxypyridin-3-yl)acrylate **80** (2.18 g, 10.52 mmol) and palladium on carbon (10%, 0.22 g) in distilled ethyl acetate (70 mL), under hydrogen at 60 psi, for 24 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute it, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure afforded the crude *ester* **100** (1.89 g, 86%) as a yellow oil; ν_{max}/cm^{-1} (film) 2925, 1736, 1657, 1590, 1467, 1412, 1312, 1251; δ_H (400 MHz, $CDCl_3$) 1.23 [3H, t, *J* 6.8, $CH_2C\underline{H}_3$], 2.61 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 2.89 [1H, t, *J* 7.6, C(3)$\underline{H}_2$], 3.96 [3H, s, $OC\underline{H}_3$], 4.11 [2H, q, *J* 6.8, $C\underline{H}_2CH_3$], 6.80 [1H, dd, *J* 7.2, 5.2, C(5')$\underline{H}$], 7.41 [1H, dd, *J* 7.2, 2.0, C(4')$\underline{H}$], 8.03 [1H, dd, *J* 4.8, 1.6, C(6')$\underline{H}$]. Compound was previously described but no spectral data was reported.[284]

Synthesis of carboxylic acids

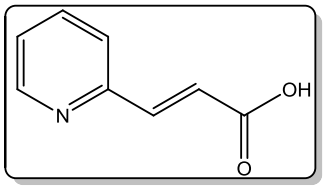


General numbering scheme for acids

The structural assignment of the α,β-unsaturated acids follows that described in the literature for analogous compounds.[96] The assignment of the saturated acids is based on 2D NMR HSQC and HMBC experiments on 3-(pyridine-3-yl)propanoic acid **47** (*Appendix V*) and by comparison with predicted ^{1}H and ^{13}C NMR signals for **47** described by Griffiths.[50]

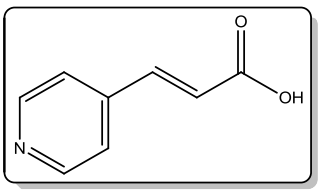
Formation of unsaturated acids

3-(Pyridine-2-yl)acrylic acid 48[46,47,285-287]



Piperidine (6 drops) was added to a solution of picolinaldehyde (32.00 g, 300 mmol) and malonic acid (31.40 g, 300 mmol) in pyridine (24.1 mL, 300 mmol) at room temperature. The reaction mixture was heated under reflux for 2.5 h, allowed to cool to room temperature with a thick brown liquid observed. The reaction mixture was washed with water (60 mL), aqueous ammonium hydroxide solution (30 mL) and acetic acid (60 mL) to generate a pale brown precipitate. The solid was isolated by suction filtration and washed with water (100 mL) to afford the crude *acid* **48** (8.73 g, 20%) as a white solid; ν_{max}/cm^{-1} (KBr) 3089, 2380 br, 1891 br, 1697, 1643, 1594, 1568, 1463, 1442, 1316, 1222, 1015, 786, 743, 701, 640, 530; δ_H (300 MHz, D_2O) 6.83 [1H, d, *J* 16.2, C(2)H], 7.34 [1H, d, *J* 16.2, C(3)H], 7.70 [1H, ddd, *J* 8.0, 6.0, 0.6, C(5')H], 7.98 [1H, d, *J* 8.1, C(3')H], 8.23 [1H, ddd, *J* 8.0, 7.8, 1.5, C(4')H], 8.53 [1H, d, *J* 5.1, C(6')H]; HRMS (ES+): Exact mass calculated for $C_8H_8NO_2$ $[M+H]^+$, 150.0555. Found 150.0558. m/z (ES+) 150.0 $[(M+H)^+$, 100%], 116.0 (6%), 114.9 (68%). Infrared spectral properties were consistent with previously reported data,[47,285] while ^{1}H NMR spectroscopy was previously run in DMSO-d_6[287] and $CDCl_3$.[286]

3-(Pyridine-4-yl)acrylic acid 50[46,286]

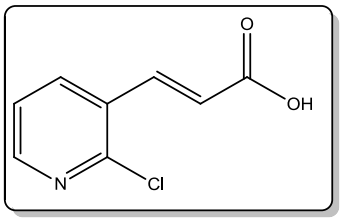


This was prepared following the procedure described for **48**, from isonicotinaldehyde (32.00 g, 300 mmol), malonic acid (31.40 g, 300 mmol), pyridine (24.1 mL, 300 mmol) and piperidine (six drops) to afford the crude *acid* **50** (28.28 g, 63%) as a yellow solid; ν_{max}/cm^{-1} (KBr) 3055, 2400 br, 1900 br, 1701, 1645, 1608, 1557, 1416, 1315, 1224, 1185, 1023, 823, 581, 522, 503; δ_H (300 MHz, D_2O) 6.81 [1H, d, *J* 16.2, C(2)H], 7.28 [1H, d, *J* 16.2, C(3)H], 7.92 [2H, d, *J* 6.9, C(3')H and C(5')H], 8.55 [2H, d, *J* 6.6, C(2')H and C(6')H]; HRMS (ES+): Exact mass calculated for

$C_8H_8NO_2$ $[M+H]^+$, 150.0555. Found 150.0558. m/z (ES+) 150.0 $[(M+H)^+$, 100%], 115.9 (6%), 114.9 (88%). Spectral properties were consistent with previously reported data.[46,286]

(*E*)-3-(2-Chloropyridin-3-yl)acrylic acid 82[41]

Method A: Knoevenagel reaction



A mixture of 2-chloronicotinaldehyde **68** (0.41 g, 2.88 mmol), malonic acid (0.33 g, 3.17 mmol), pyridine (15 mL) and piperidine (six drops) was heated under reflux for 3 h and the reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure to furnish the crude *acid* as a dark yellow solid Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) provided the pure *unsaturated acid* **82** (0.12 g, 23%) as an off-white solid; ν_{max}/cm^{-1} (KBr) 3000–2800 (COOH), 2925, 1740, 1690, 1626, 1577, 1559, 1431, 1397, 1283, 1229, 1063, 990, 803, 736, 673; δ_H (300 MHz, DMSO-d_6) 6.71 [1H, d *J* 15.9, C(2)H], 7.50 [1H, dd, *J* 7.8, 4.5, C(5')H], 7.76 [1H, d, *J* 15.9, C(3)H], 8.38 [1H, dd, *J* 7.8, 1.8, C(4')H], 8.44 [1H, dd, *J* 4.8, 2.1, C(6')H]. ^{1}H NMR spectral data for **82** is consistent with the reported spectrum which was recorded in $CDCl_3$.[41]

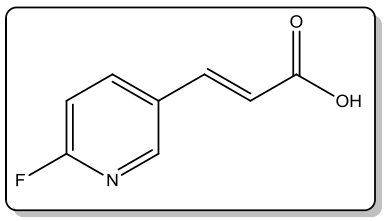
Method B: Hydrolysis[41]

Aqueous sodium hydroxide (1.0 M, 38.3 mL, 38.32 mmol) was added to a solution of (*E*)-ethyl 3-(2-chloropyridin-3-yl)acrylate **75** (5.39 g, 25.48 mmol) in methanol (50 mL) and the reaction mixture was stirred for 1 h at 50 °C. The reaction mixture was diluted with TBME (30 mL) and brine (30 mL) to give an aqueous and organic layer. The layers were separated and the organic layer was extracted with aqueous sodium hydroxide (1.0 M, 3 × 30 mL). The aqueous extracts were combined, acidified to pH = 2 by addition of aqueous hydrochloric acid (3.2 M), followed by extraction with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated under reduced pressure to give the crude *acid* **82** (3.97 g, 85%) as a white solid.* Spectral properties were consistent with data reported from method A above.

* Spectrum contains ethyl acetate as well as 5 mol% of aldehyde **68** from earlier step.

(*E*)-3-(6-Fluoropyridin-3-yl)acrylic acid 110[119]

Note: The microwave reaction was carried out in a sealed tube with stirring, with an initial power input of 200 W. On reaching the desired temperature, the power decreases automatically to maintain the set temperature.

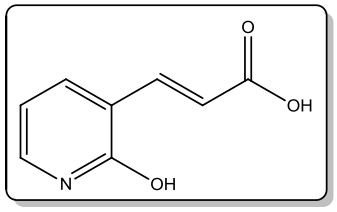


This procedure is based on a method employed by Foley[2] which was originally described by Baudoin.[123] 5-Bromo-2-fluoropyridine (1.00 g, 5.68 mmol, palladium(II) acetate (0.02 g), tri(*o*-tolyl)phosphine (0.06 g, 0.27 mmol), triethylamine (2.0 mL, 14.26 mmol) and acrylic acid (0.5 mL, 7.04 mmol) were placed in a 10 mL microwave reaction vessel and this was sealed. The reaction mixture was stirred and heated for 5 min at 200 W at 100 °C, followed by stirring and heating for 6 min at 300 W at 100 °C. The crude reaction mixture was cooled to room temperature and the pressure released by piercing the cap with a needle.

The crude mixture was washed with aqueous saturated sodium bicarbonate (20 mL) and filtered through a plug of Celite®. The filtrate was then acidified with aqueous hydrochloric acid (3.2 M, 15 mL) to generate a precipitate which was isolated by suction filtration to provide the crude *acid* **110** (1.06 g, quantitative yield) as a light brown solid; ν_{max}/cm^{-1} (KBr) 3500–2900 (COOH), 2921, 1673, 1634, 1588, 1490, 1440, 1340, 1250, 1024, 991, 829; δ_H (300 MHz, DMSO-d_6), 6.66 [1H, d, *J* 16.2, C(2)H], 7.25 [1H, dd, *J* 8.7, 3.0, C(4')H], 7.63 [1H, d, *J* 15.9, C(3)H], 8.38 [1H, ddd, *J* 8.4, 8.3, 2.4, C(5')H], 8.55 [1H, d, *J* 2.4, C(2')H]. No spectral data was reported for this compound though it was previously described by Denonne and co-workers.[119]

Note: The procedure was carried out five times using this reaction scale with the combined yields of each reaction making up the final sample used in the subsequent reaction.

(*E*)-3-(2-Hydroxypyridin-3-yl)acrylic acid 114[96]



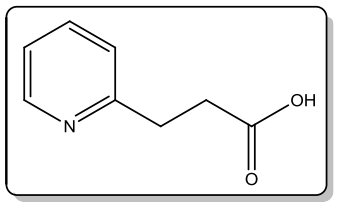
This was prepared following the procedure described for **82**, from pyridone tautomer of 2-hydroxynicotinaldehyde **74** (1.95 g, 15.83 mmol) and malonic acid (1.81 g, 17.41 mmol) in pyridine (20 mL) and piperidine (six drops) to furnish the crude *acid* as a dark yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) provided the crude *acid* **114** (2.63 g, quantitative yield) as a brown solid; m.p. 290–291 °C (lit.,[96] >250 °C); ν_{max}/cm^{-1} (KBr) 3500–2500 (COOH), 2924, 1665, 1617, 1554, 1459, 1317, 1292, 1254, 1212, 1186, 982, 773; δ_H (400 MHz, DMSO-d_6)* 6.30 [1H, dd, *J* 6.8, 6.4, C(5')H], 6.99 [1H, d, *J* 16.0, C(2)H], 7.44–7.50 [2H, m, C(6')H and C(3)H], 7.81 [1H, dd, *J* 7.2, 1.6, C(4')H]. Spectral properties were consistent with previously reported data.[96]

* Sample contains ~34 mol% unknown impurity which is determined by comparative integration of doublet of doublets at δ_H 6.30 and 7.39 ppm but this may not be correct. Signals for the unknown impurity in the ^{1}H NMR spectrum of **114** are δ_H 7.39 [0.5H, dd, *J* 7.6, 5.6], 7.78 [0.2H, apparent t, *J* 7.6], 8.58 [0.7H, d, *J* 4.0]. In spite of the presence of this impurity, the material was brought forward without further purification. Purification by Trecourt and co-workers involved crystallisation from methanol but this was not followed in this work.[96]

Preparation of saturated acids

3-(Pyridin-2-yl)propanoic acid 46[37,288]

Method A: Hydrogenation



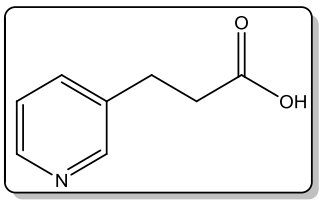
This was prepared following the procedure described for **99**, from acid **48** (1.70 g, 11.25 mmol) and palladium on carbon (10%, 0.40 g) in distilled ethyl acetate (70 mL), under hydrogen at 60 psi for 48 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure gave the crude *acid* **46** (1.52 g, 90%) as a white crystalline solid; m.p. 137 °C (lit.,[288] 141 °C); δ_H (300 MHz, D_2O) 2.60 [2H, t, *J* 7.2, C(2)H_2], 3.14 [2H, t, *J* 7.2, C(3)H_2], 7.65–7.78 [2H, m, C(3')H and C(5')H], 8.30 [1H, ddd, *J* 8.1, 8.0, 1.5, C(4')H], 8.48

[1H, br d with further unresolved splitting, *J* ~6.0, C(6')H]; HRMS (ES+): Exact mass calculated for $C_8H_{10}NO_2$ $[M+H]^+$, 152.0712. Found 152.0717. m/z (ES+) 152.1 $[(M+H)^+$, 74%], 115.1 (66%). Physical properties were consistent with previously reported data.[288]

Method B: Hydrolysis
This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ester **43** (5.05 g, 28.21 mmol) in methanol (70 mL) and aqueous sodium hydroxide (1.0 M, 42.2 mL, 42.20 mmol) to furnish the crude *acid* as a white solid **46** (4.43 g, quantitative yield); ν_{max}/cm^{-1} (KBr) 3400–2800 (COOH), 2926, 1739, 1700, 1634, 1616, 1540, 1446, 1387, 1180, 796, 762; δ_H (400 MHz, DMSO-d_6) 2.84 [2H, apparent td, *J* 7.2, 2.4, C(2)H_2], 3.22 [2H, apparent td, *J* 7.2, 2.8, C(3)H_2], 7.71–7.80 [1H, m, C(3')H or C(5')H], 7.81–7.90 [1H, m, C(3')H or C(5')H], 8.29–8.40 [1H, m, C(4')H], 8.71 [1H, d with further unresolved splitting, *J* 3.2, C(6')H].

3-(Pyridin-3-yl)propanoic acid 47[37,45,289]

Method A: Hydrogenation



This was prepared following the procedure described for **99**, from 3-(pyridin-3-yl)acrylic acid (1.70 g, 11.25 mmol) and palladium on carbon (10%, 0.40 g) in distilled ethyl acetate (70 mL), under hydrogen at 60 psi for 48 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure furnished the crude *acid* **47** (1.45 g, 86%) as a white solid; m.p. 149–150 °C (lit.,[289] 147–150 °C); δ_H (300 MHz, D_2O)* 2.50 [2H, t, *J* 7.5, C(2)H_2], 2.97 [2H, t, *J* 7.5, C(3)H_2], 7.80 [1H, dd, *J* 8.1, 6.0, C(5')H], 8.29 [1H, d, *J* 8.4, C(4')H], 8.43–8.52 [2H, m contains overlapping d and s, C(2')H and C(6')H]; HRMS (ES+): Exact mass calculated for $C_8H_{10}NO_2$ $[M+H]^+$, 152.0712. Found 152.0718. m/z (ES+) 152.1 $[(M+H)^+$, 100%], 150.0 (12%), 115.0 (40%). ^{1}H NMR Spectral properties were consistent with data previously reported in $CDCl_3$.[45]

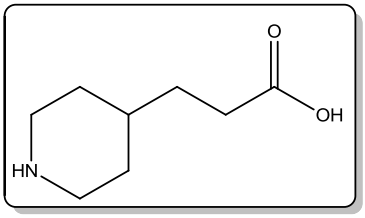
* Sample contains ~14 mol% unsaturated acid starting material.

Method B: Hydrolysis
This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ester **44** (8.49 g, 47.38 mmol) in methanol (70 mL) and aqueous sodium hydroxide (1.0 M, 71.1 mL, 71.10 mmol) to furnish the crude *acid* **47** as a white solid (7.76 g, quantitative yield); ν_{max}/cm^{-1} (KBr) 3600–2900 (COOH), 1720, 1618, 1560, 1468, 1413, 1166.; δ_H (400 MHz, DMSO-d_6) 2.70 [2H, t, *J* 7.6, C(2)H_2]*, 3.01 [2H, t, *J* 7.2, C(3)H_2]*, 7.93–8.01 [1H, m, C(5')H], 8.49 [1H, d with further unresolved splitting, *J* 8.0, C(4')H], 8.76 [1H, d, *J* 5.2, C(6')H], 8.83 [1H, s, C(2')H]; δ_C (125.8 Hz, DMSO-d_6)** 27.1 [CH_2, C(3)H_2], 33.9 [CH_2, C(2)H_2], 126.2 [CH, C(5')H], 140.7, 142.6, 144.2 [3 × CH, C(2')H, C(4')H and C(6')H], 173.2 [C, C(1)=O]. Assignment of C(2)H_2 and C(3)H_2 groups in both ^{1}H and ^{13}C NMR spectra was aided by HSQC and HMBC 2D NMR experiments (*Appendix V*). This serves as the basis for assignment of C(2)H_2 and C(3)H_2 signals in the ^{1}H and ^{13}C NMR

spectra of analogous saturated esters and acids. Spectral data was consistent with that described by Griffiths.[50]

* Integration is higher than expected.
** Quaternary carbon C(3') not detected in ^{13}C NMR spectrum.

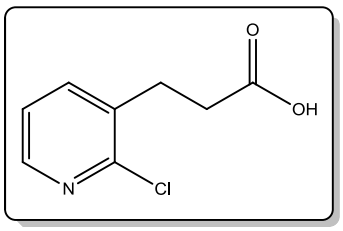
Attempted hydrogenation of 3-(pyridine-4-yl)acrylic acid 50



Hydrogenation was attempted following the procedure described for **99**, from acid **50** (2.00 g, 13.40 mmol) and palladium on carbon (10%, 0.40 g) in distilled ethyl acetate (70 mL), under hydrogen at 60 psi, for 48 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute it, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure yielded the crude product **51** as a white solid (1.35 g, 64% based on assumption of 3-(piperidin-4-yl)propanoic acid as product). The crude product **51** is assumed to resemble 3-(piperidin-4-yl)propanoic acid as there is literature precedent for hydrogenation of acid **50** to proceed beyond saturation of the alkene.[49,290] However, previous work has provided the corresponding hydrochloride salt following hydrogenation of **50** due to the presence of a chlorine source either during or after the reaction. While there is spectroscopic data for the hydrochloride salt,[290] there is no published data attributed to the free acid. δ_H (300 MHz, D_2O) for white solid* 1.18–1.34 [2H, m, one of C(3')$\underline{H}_2$ or C(5')$\underline{H}_2$], 1.46 [3H, t, *J* 6.0, one of C(3')$\underline{H}_2$ or C(5')$\underline{H}_2$ and C(4')$\underline{H}$], 1.84 [2H, br d, *J* 14.1, one of C(2')$\underline{H}_2$ or C(6')$\underline{H}_2$], 2.10 [2H, t, *J* 7.5, one of C(2')$\underline{H}_2$ or C(6')$\underline{H}_2$], 2.86 [2H, ddd, *J* 12.6, 9.9, 3.0, C(2)$\underline{H}_2$ or C(3)$\underline{H}_2$], 3.29 [2H, br d with further unresolved splitting, *J* 12.9, C(2)$\underline{H}_2$ or C(3)$\underline{H}_2$].

* The ^{1}H NMR signals of **51** are tentatively assigned.

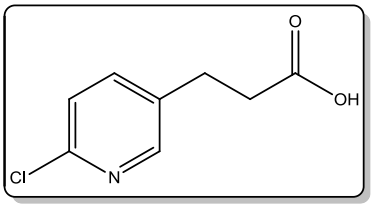
3-(2-Chloropyridin-3-yl)propanoic acid 101



This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ethyl 3-(2-chloropyridin-3-yl)propanoate **81** (4.01 g, 19.10 mmol) in methanol (40 mL) and aqueous sodium hydroxide (1.0 M, 28.7 mL, 28.70 mmol) to give the crude *acid* **101** (2.44 g, 69%) as a white solid; m.p. 126–128 °C; ν_{max}/cm^{-1} (KBr) 3000–2400 (COOH), 1731, 1715, 1585, 1432, 1400, 1300, 1270, 1205, 1184, 1087, 811; δ_H (300 MHz, $CDCl_3$) 2.76 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 3.07 [2H, t, *J* 7.2, C(3)$\underline{H}_2$], 7.20 [1H, dd, *J* 7.6, 4.8, C(5')$\underline{H}$], 7.64 [1H, dd, *J* 7.6, 2.0, C(4')$\underline{H}$], 8.27 [1H, dd, *J* 4.4, 1.6, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 28.1 [CH_2, $\underline{C}$(3)H_2], 32.8 [CH_2, br, $\underline{C}$(2)H_2], 122.7 [CH, $\underline{C}$(5')H], 134.4 [C, $\underline{C}$(3')], 139.4 [CH, $\underline{C}$(4')H], 147.8 [CH, $\underline{C}$(6')H], 151.1 [C, $\underline{C}$(2')Cl], 177.3 [C, $\underline{C}$(1)=O]*; HRMS (ES+): Exact mass calculated for $C_8H_9{}^{37}ClNO_2$ $[M+H]^+$, 188.0292. Found 188.0304 and exact mass calculated for $C_8H_9{}^{35}ClNO_2$ $[M+H]^+$, 186.0329. Found 186.0322. m/z 188.0 {[$(C_8H_9{}^{37}ClNO_2)^+$], 35%}, 186.0 {[$(C_8H_9{}^{35}ClNO_2)^+$], 100%}, 115.0 (56%), 104.9 (10%), 73.9 (38%).

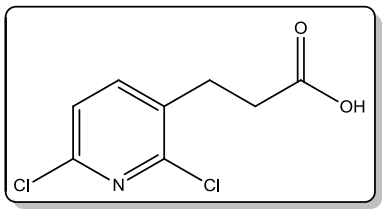
* Signal for $\underline{C}$(1)=O is tentatively assigned.

3-(6-Chloropyridin-3-yl)propanoic acid 102



This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ethyl 3-(6-chloropyridin-3-yl)propanoate **93** (2.65 g, 12.38 mmol) in methanol (40 mL) and aqueous sodium hydroxide (1.0 M, 18.6 mL, 18.60 mmol) to afford the crude *acid* **102** (1.31 g, 57%) as a white solid; m.p. 97–99 °C; (Found C, 51.81; H, 4.30; N, 7.44; $C_8H_8ClNO_2$. requires C, 51.77; H, 4.34; N, 7.55%); ν_{max}/cm^{-1} (KBr) 3700–2800 (COOH), 2923, 1701, 1588, 1565, 1465, 1435, 1318, 1220, 1103, 834; δ_H (300 MHz, $CDCl_3$) 2.69 [2H, t, *J* 7.2, C(2)$\underline{H}_2$], 2.96 [2H, t, *J* 7.2, C(3)$\underline{H}_2$], 7.27 [1H, d, *J* 8.1, C(5')$\underline{H}$], 7.55 [1H, dd, *J* 8.1, 2.4, C(4')$\underline{H}$], 8.30 [1H, d, *J* 2.1, C(2')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 27.0 [CH_2, $\underline{C}(3)H_2$], 34.8 [CH_2, $\underline{C}(2)H_2$], 124.2 [CH, $\underline{C}$(5')H], 134.8 [C, $\underline{C}$(3')], 139.1 [CH, $\underline{C}$(4')H], 149.37 [C, $\underline{C}$(6')Cl], 149.42 [CH, $\underline{C}$(2')H], 176.9 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_8H_9{}^{35}ClNO_2$ $[M+H]^+$, 186.0322. Found 186.0320. m/z 188.2 {[$(C_8H_9{}^{37}ClNO_2)^+$], 34%}, 186.2 {[$(C_8H_9{}^{35}ClNO_2)^+$], 100%}.

3-(2,6-Dichloropyridin-3-yl)propanoic acid 103[118]

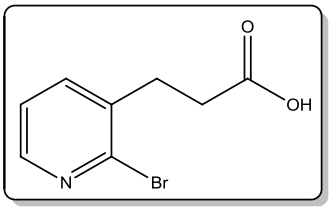


This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ethyl 3-(2,6-dichloropyridin-3-yl)propanoate **94** (1.00 g, 4.00 mmol) in methanol (40 mL), aqueous sodium hydroxide (1.0 M, 6.0 mL, 6.00 mmol). The reaction mixture was diluted with ethyl acetate (30 mL) and brine (30 mL) to give an aqueous and organic layer. The layers were separated and the organic layer was extracted with aqueous sodium hydroxide (1.0 M, 3 × 30 mL). The aqueous layers were combined, acidified to pH = 2 by addition of aqueous hydrochloric acid (3.2 M), followed by extraction with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated under reduced pressure to give the crude *acid* as a white solid. A strong smell of acetic acid was observed from the crude product and this was confirmed by ^{1}H NMR analysis.* Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *saturated acid* **103** (0.49 g, 51%) as a white solid; m.p. 153–156 °C (lit.,[118] 155–157 °C); (Found C, 43.69; H, 3.15; N, 6.12; Cl, 32.16 $C_8H_7NO_2Cl$. requires C, 43.66; H, 3.21; N, 6.37; Cl, 32.22%); ν_{max}/cm^{-1} (KBr) 3600–2900 (COOH), 2953, 1702, 1654, 1637, 1552, 1429, 1311, 1221, 1137, 1078, 836; δ_H (400 MHz, $CDCl_3$) 2.74 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 3.03 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 7.23 [1H, d, *J* 8.0, C(5')$\underline{H}$], 7.60 [1H, d, *J* 8.0, C(4')$\underline{H}$]; δ_C (150.9 MHz, $CDCl_3$) 27.4 [CH_2, $\underline{C}(3)H_2$], 32.5 [CH_2, $\underline{C}(2)H_2$], 123.2 [CH, $\underline{C}$(5')H], 133.0 [C, $\underline{C}$(3')], 141.5 [CH, $\underline{C}$(4')H], 148.5 [C, $\underline{C}$(2')Cl or $\underline{C}$(6')Cl], 150.1 [C, $\underline{C}$(2')Cl or $\underline{C}$(6')Cl], 176.7 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_8H_8{}^{35}Cl_2NO_2$ $[M+H]^+$, 219.9932. Found 219.9935. m/z (ES+) 222.1 {[$(C_8H_8{}^{37}Cl^{35}ClNO_2)^+$], 32%}, 220.1 {[$(C_8H_8{}^{35}Cl_2NO_2)^+$], 54%}. Melting point analysis was consistent with previously reported data.[118]

* The presence of acetic acid results from use of ethyl acetate in initial step of the workup instead of TBME and is due to basic hydrolysis of ethyl acetate followed by acidification. This was also observed in the attempted hydrolysis of ethyl 3-(2-fluoropyridin-3-yl)propanoate **99** to form **105**.

Single crystals of 3-(2,6-dichloropyridin-3-yl)propanoic acid **103** were grown from deuterated chloroform. Crystal data: $C_8H_7Cl_2NO_2$, M = 220.05, monoclinic, $P2_1/c$, a = 17.022(3) Å, b = 4.6952(8) Å, c = 12.127(2) Å, β = 101.411(6)°, V = 950.1(3) Å^3, Z = 4, D_c = 1.538 g cm^{-3}, F_{000} = 448, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.03°, μ = 0.647 mm^{-1}, 8470 reflections collected, 1682 unique (R_{int} = 0.1113), final GooF = 0.915, R_1 = 0.0376, wR_2 = 0.0878 (1154obs. data: $I > 2\sigma(I)$); R_1 = 0.0586, wR_2 = 0.0952 (all data). Full details are given in *Appendix III*.

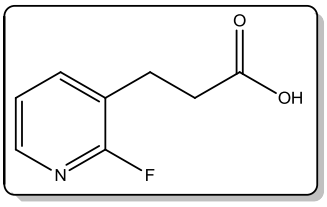
3-(2-Bromopyridin-3-yl)propanoic acid 104



This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ethyl 3-(2-bromopyridin-3-yl)propanoate **95** (from Method B: Hydrogenation using Wilkinson's catalyst) (2.26 g, 8.77 mmol) in methanol (40 mL) and aqueous sodium hydroxide (1.0 M, 13.2 mL, 13.16 mmol) to furnish the crude *acid* **104** as a white solid (1.65 g, 82%); m.p. 145–148 °C; ν_{max}/cm^{-1} (KBr) 3500–2300 (COOH), 2921, 1726, 1638, 1405, 1368, 1299, 1204, 1079, 1057, 811, 657; δ_H (300 MHz, $CDCl_3$) 2.76 [2H, t, J 7.6, C(2)$\underline{H}_2$], 3.06 [2H, t, J 7.6, C(3)$\underline{H}_2$], 7.22 [1H, dd, J 7.6, 4.8, C(5')$\underline{H}$], 7.60 [1H, dd, J 7.6, 1.8, C(4')$\underline{H}$], 8.26 [1H, dd, J 4.8, 2.1, C(6')$\underline{H}$]; δ_C (150.9 MHz, $CDCl_3$) 30.2 [CH_2, $\underline{C}$(3)H_2], 32.7 [CH_2, $\underline{C}$(2)H_2], 123.0 [CH, $\underline{C}$(5')H], 136.8 [C, $\underline{C}$(2')Br or $\underline{C}$(3')], 138.8 [CH, $\underline{C}$(4')H], 144.2 [C, $\underline{C}$(2')Br or $\underline{C}$(3')], 148.3 [CH, $\underline{C}$(6')H], 176.1 [C, $\underline{C}$(1)=O]; HRMS (ES+)*: Exact mass calculated for $C_8H_9{}^{79}BrNO_2$ $[M+H]^+$, 229.9817. Found 229.9819. m/z (ES+) 232.0 {[($C_8H_9{}^{81}BrNO_2$)$^+$], 100%}, 230.0 {[($C_8H_9{}^{79}BrNO_2$)$^+$], 90%}, 209.2 (37%).

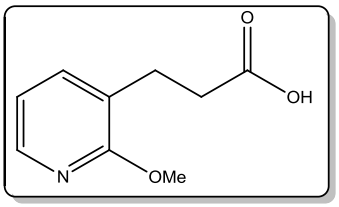
* Mass spectrometry was obtained on impure sample of **104** arising from attempted hydrolysis of ester **95** (from Method A: $NaBH_4$/Cu(I)Cl reduction).

3-(2-Fluoropyridin-3-yl)propanoic acid 105[119]



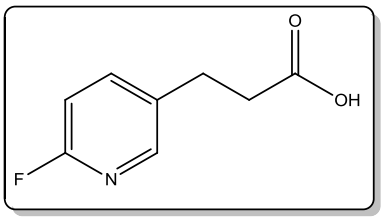
This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ester **99** (2.31 g, 11.71 mmol) in methanol (50 mL) and aqueous sodium hydroxide (1.0 M, 17.6 mL, 17.60 mmol). Following use of ethyl acetate in the workup a strong smell of acetic acid was observed from the crude product and this was confirmed by ^{1}H NMR analysis as previously observed for **103**. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *saturated acid* **105** (1.05 g, 53%) as a white solid; m.p. 100–102 °C; ν_{max}/cm^{-1} (KBr) 3700–2500 (COOH), 2917, 1733, 1613, 1583, 1457, 1440, 1194, 1183, 813; δ_H (300 MHz, $CDCl_3$) 2.73 [2H, t, J 7.2, C(2)$\underline{H}_2$], 2.98 [2H, t, J 7.5, C(3)$\underline{H}_2$], 7.14 [1H, ddd, J 7.2, 5.1, 1.8, C(5')$\underline{H}$], 7.67 [1H, ddd, J 9.6, 7.5, 2.1, C(4')$\underline{H}$], 8.10 [1H, apparent dt, J 4.8, 1.5, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 24.1 [CH_2, d, $^3J_{CF}$ 1.9, $\underline{C}$(3)H_2], 33.1 [CH_2, $\underline{C}$(2)H_2], 121.6 [CH, d, $^4J_{CF}$ 4.3, $\underline{C}$(5')H], 122.0 [C, d, $^2J_{CF}$ 30.2, $\underline{C}$(3')], 141.2 [CH, d, $^3J_{CF}$ 5.7, $\underline{C}$(4')H], 145.7 [CH, d, $^3J_{CF}$ 14.4, $\underline{C}$(6')H], 162.0 [C, d, $^1J_{CF}$ 239.1, $\underline{C}$(2')F], 177.2 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_8H_9FNO_2$ $[M+H]^+$, 170.0617. Found 170.0614. m/z (ES+) 170.0 [$(M+H)^+$, 100%], 82.9 (52%). No spectral data was reported for this compound though it was previously described by Denonne and co-workers.[119]

3-(2-Methoxypyridin-3-yl)propanoic acid 106[119]



This was prepared following the procedure described for **82** (Method B: Hydrolysis), from a solution of ethyl 3-(2-methoxypyridin-3-yl)propanoate **100** (1.89 g, 9.01 mmol) in methanol (40 mL) and aqueous sodium hydroxide (1.0 M, 13.5 mL, 13.50 mmol) to yield the crude *acid* **106** as a white solid (0.95 g, 58%); m.p. 112–114 °C; ν_{max}/cm^{-1} (KBr) 3500–2200 (COOH), 2959, 2929, 1726, 1603, 1590, 1478, 1416, 1288, 1200, 1186, 1171, 1118, 1022, 802, 775; δ_H (300 MHz, $CDCl_3$) 2.68 [2H, t, *J* 7.6, C(2)$\underline{H}_2$], 2.90 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 3.96 [3H, s, OC$\underline{H}_3$], 6.81 [1H, dd, *J* 6.8, 4.8, C(5')$\underline{H}$], 7.43 [1H, dd, *J* 7.2, 2.0, C(4')$\underline{H}$], 8.05 [1H, dd, *J* 5.2, 2.0, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 24.4 [CH_2, $\underline{C}$(3)H_2], 32.9 [CH_2, br, $\underline{C}$(2)H_2], 53.3 [CH_3, O$\underline{C}H_3$], 116.7 [CH, $\underline{C}$(5')H], 122.7 [C, $\underline{C}$(3')], 138.1 [CH, $\underline{C}$(4')H], 144.9 [CH, $\underline{C}$(6')H], 162.1 [C, $\underline{C}$(2')OCH_3], 177.8 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_9H_{12}NO_3$ $[M+H]^+$, 182.0817. Found 182.0821. m/z (ES+) 181.1 $[(M+H)^+$, 100%]. No spectral data was reported for this compound though it was previously described by Denonne and co-workers.[119]

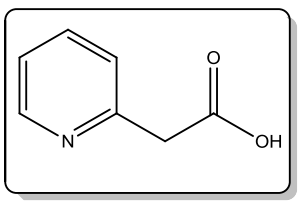
3-(6-Fluoropyridin-3-yl)propanoic acid 115[119]



This was prepared following the procedure described for **99**, from (*E*)-3-(6-fluoropyridin-3-yl)acrylic acid **110** (2.67 g, 15.90 mmol) and palladium on carbon (10%, 0.26 g) in distilled ethyl acetate (70 mL), under hydrogen at 50 psi for 18 h at room temperature. The reaction mixture was filtered through a plug of Celite® to remove the catalyst followed by an ethanol rinse (2 × 50 mL) of the Celite® bed to fully elute the product, while keeping the catalyst wet. Concentration of the filtrate under reduced pressure gave the crude *acid* **115** (1.19 g, 44%) as a dark red solid; m.p. 83–87 °C; ν_{max}/cm^{-1} (KBr) 3500–2500 (COOH), 2939, 1714, 1604, 1488, 1398, 1252, 837; δ_H (400 MHz, $CDCl_3$)* 2.70 [2H, t, *J* 7.2, C(2)$\underline{H}_2$], 2.97 [2H, t, *J* 7.6, C(3)$\underline{H}_2$], 6.89 [1H, dd, *J* 8.4, 2.8, C(4')$\underline{H}$], 7.70 [1H, ddd, *J* 8.0, 8.0, 2.4, C(5')$\underline{H}$], 8.11 [1H, d, *J* 1.6, C(2')$\underline{H}$], 10.37 [1H, br s, $CO_2\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 26.8 [CH_2, $\underline{C}$(3)H_2], 35.1 [CH_2, $\underline{C}$(2)H_2], 109.4 [CH, d, $^2J_{CF}$ 37.0, $\underline{C}$(5')H], 133.3 [C, d, $^4J_{CF}$ 4.5, $\underline{C}$(3')], 141.3 [CH, d, $^3J_{CF}$ 8.3, $\underline{C}$(4')H], 147.0 [CH, d, $^3J_{CF}$ 14.3, $\underline{C}$(2')H], 162.5 [C, d, $^1J_{CF}$ 239.0, $\underline{C}$(6')F], 178.0 [C, $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_8H_9FNO_2$ $[M+H]^+$, 170.0619. Found 170.0617. m/z (ES+) 170.0 $[(M+H)^+$, 100%]. No spectral data was reported for this compound though it was previously described by Denonne and co-workers.[119]

* Sample contains ethyl acetate.

2-(Pyridin-2-yl)acetic acid 108[121]

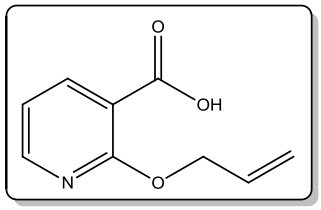


Aqueous potassium hydroxide (1.0 M, 45.4 mL, 45.41 mmol) was added to a solution of methyl 2-(pyridin-2-yl)acetate **107** (5.00 g, 30.27 mmol) in ethanol (40 mL) at room temperature. The reaction mixture was stirred at 50 °C for 2 h after which the reaction mixture was bright orange. The reaction mixture was allowed to cool to room temperature, and then the reaction mixture was concentrated to one-

third of its original volume and diluted with ether (3 × 20 mL). The layers were separated and the aqueous layer was subsequently neutralised by slow addition of aqueous hydrochloric acid (3.2 M) and confirmation of neutralisation by universal indicator paper. The mixture was concentrated *in vacuo* to give the crude *acid* **108** possibly as the hydrochloride salt **108·HCl** (4.67 g, quantitative yield based on carboxylic acid, 89% based on hydrochloride salt) as a pale orange solid; m.p. 149–150 °C (lit.,[121] 98 °C); ν_{max}/cm^{-1} (KBr) 3400–3100 (COOH), 1586, 1480, 1437, 1373; δ_H (400 MHz, DMSO-d_6) 3.43 [2H, s, C(2)$\underline{H}_2$], 7.10 [1H, ddd, *J* 7.2, 5.0, 0.8, C(5')$\underline{H}$], 7.29 [1H, d, *J* 7.6, C(3')$\underline{H}$], 7.61 [1H, ddd, *J* 7.8, 7.6, 2.0, C(4')$\underline{H}$], 8.37 [1H, dd, *J* 4.8, 0.8, C(6')$\underline{H}$]. ^{1}H NMR spectral properties were not consistent with previously reported data using DMSO-d_6 as solvent.[121] The melting point obtained was higher than with previously reported, accordingly it is likely that the product is isolated as the hydrochloride salt; m.p. (lit.,[122] 135–137 °C).

Synthesis of substituted 3-pyridylcarboxylic acids

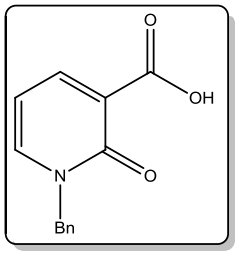
2-(Allyloxy)nicotinic acid 117[125]



2-Chloronicotinic acid **57** (5.00 g, 31.74 mmol) was added in five equal portions to a suspension of sodium hydride (2.10 g, 60% mineral dispersion, 87.47 mmol) in dry dimethylformamide [(DMF), (70 mL)] stirring at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. 2-Propenol (2.4 mL, 35.23 mmol) was then added dropwise and the reaction mixture was warmed to room temperature over 3 h; then heated to 80 °C for 16 h. The reaction mixture was allowed to cool to room temperature, then the resulting light brown mixture was poured onto aqueous hydrochloric acid (3.2 M, 100 mL) and stirred for 5 min. The layers were separated and the aqueous layer was extracted with ether (4 × 100 mL). The combined organic extracts were washed with brine (40 mL), dried using magnesium sulfate and concentrated *in vacuo* to afford the crude *acid* as a yellow oil. Since there was residual DMF present in the crude product, a further workup involved reacidification (50 mL), separation of layers and extraction of the aqueous layer with ether (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried and concentrated *in vacuo* to provide the crude *acid* **117*** as a white solid (4.65 g, 82%); m.p. 160–162 °C; ν_{max}/cm^{-1} (KBr) 3500–2700 (COOH), 2945, 1702, 1686, 1591, 1577, 1441, 1421, 1313, 1278, 1241, 994, 781; δ_H (400 MHz, $CDCl_3$) 5.12 [2H, dt, *J* 6.0, 1.2, OC$\underline{H}_2$CHCH_2], 5.38 [1H, dd with further unresolved splitting, *J* 10.2, 0.9, one of OCH_2CHC$\underline{H}_2$], 5.48 [1H, dd with further unresolved splitting, *J* 17.1, 1.2, one of OCH_2CHC$\underline{H}_2$], 6.05–6.22 [1H, m, OCH_2C$\underline{H}$CH_2], 7.13 [1H, dd, *J* 7.5, 4.8, C(5')$\underline{H}$], 8.38 [1H, dd, *J* 4.8, 1.8, C(6')$\underline{H}$], 8.47 [1H, dd, *J* 7.5, 2.1, C(4')$\underline{H}$].

* In retrospect it was discovered that the spectral data assigned by Liu *et al.*[125] corresponds to the *N*-allyl acid **119** and not the *O*-allyl acid **117** as reported.

1-Benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid 122[126]

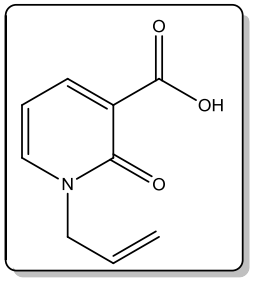


2-Hydroxynicotinic acid **118** (3.00 g, 21.56 mmol) was added portionwise to a stirring solution of potassium hydroxide (2.86 g, 43.40 mmol) and water/methanol (7:1 ratio, 35/5 mL) at 0 °C. Neat benzyl bromide (5.2 mL, 43.7 mmol) was added dropwise and the reaction mixture was heated under reflux for 6.5 h initially. After this time, additional anhydrous potassium hydroxide (1.30 g, 19.7 mmol) was added in one portion and the reaction mixture was heated under reflux for a further 2 h. After cooling to room temperature, the solution was evaporated to half of the original volume and acidified with aqueous hydrochloric acid solution (3.2 M, 25 mL) to generate a precipitate. The yellow precipitate was isolated by suction filtration to give the crude *acid*. ^{13}C NMR spectroscopy of the crude *acid* afforded signals at δ_C 53.2 and 65.4 ppm, which is indicative of both the *N*-benzyl acid **122** and the *O*-benzyl acid **121** respectively.[136,137] Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) to (100:0) gave the pure N-*benzylated acid* **122** (2.23 g, 70%) as a white solid; m.p. 125–128 °C (lit.,[125] 130 °C); ν_{max}/cm^{-1} (KBr) 3500–3000 (COOH), 3423, 3065, 1734, 1731, 1630 w (C=O pyridone), 1567, 1480, 1456, 1435, 773; δ_H (400 MHz, $CDCl_3$)* 5.27 [2H, s, NC$\underline{H}_2$C$_6$H$_5$], 6.54 [1H, dd, *J* 6.8, 6.8, C(5')$\underline{H}$], 7.29–7.44 [5H, m, 5 × aromatic $\underline{H}$], 7.63 [1H, dd, *J* 6.8, 2.0, C(6')$\underline{H}$], 8.51 [1H, dd, *J* 7.2, 2.4, C(4')$\underline{H}$], 14.26 [1H, s, CO$_2\underline{H}$]; δ_C (150.9 MHz, $CDCl_3$) 53.2 [CH_2, N$\underline{C}$H$_2$C$_6$H$_5$], 108.4 [CH, $\underline{C}$(5')H], 118.6 [C, $\underline{C}$(3')], 128.4 [CH, 2 × aromatic $\underline{C}$H], 129.0 [CH, aromatic $\underline{C}$H], 129.4 [CH, 2 × aromatic $\underline{C}$H], 134.3 [C, aromatic $\underline{C}$], 142.0 [CH, $\underline{C}$(6')H], 145.7 [CH, $\underline{C}$(4')H], 164.2 [C, $\underline{C}$(2')=O or $\underline{C}$(1)=O], 165.4 [C, $\underline{C}$(2')=O or $\underline{C}$(1)=O]; HRMS (ES+): Exact mass calculated for $C_{13}H_{12}NO_3$ $[M+H]^+$, 230.0811. Found 230.0817. m/z (ES+) 230.4 $[(M+H)^+$, 100%]. ^{1}H NMR and ^{13}C NMR assignment is by analogy with HMBC and HSQC 2D NMR experiments for *N*-allyl acid **119**.

Single crystals of 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **122** were grown from deuterated chloroform. Crystal data: $C_{13}H_{11}NO_3$, M = 229.23, monoclinic, $P2_1/n$, a = 4.2977(6) Å, b = 35.811(5) Å, c = 7.4865(11) Å, β = 97.073(4)°, V = 1143.4(3) Å^3, Z = 4, D_c = 1.332 g cm^{-3}, F_{000} = 480, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.04°, μ = 0.096 mm^{-1}, 7133 reflections collected, 2002 unique (R_{int} = 0.0303), final GooF = 1.759, R_1 = 0.0579, wR_2 = 0.1325 (1558 obs. data: $I > 2\sigma(I)$); R_1 = 0.0734, wR_2 = 0.1361 (all data). Full details are given in *Appendix III*.

* In retrospect it was discovered that the spectral data reported by Liu corresponds to the *N*-benzyl acid **122** and not the *O*-benzyl acid **121** as stated in that work.[125]

1-Allyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid 119

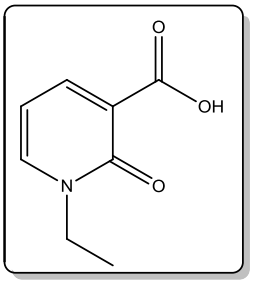


This was prepared following the procedure described for **122**, from a solution of potassium hydroxide (2.86 g, 43.40 mmol) in water/methanol (35/5 mL), 2-hydroxynicotinic acid **118** (3.00 g, 21.57 mmol) and allyl bromide (3.8 mL, 43.70 mmol) to give the crude N-*allyl acid* **119*** as a white solid (5.36 g, quantitative yield); ν_{max}/cm^{-1} (KBr) 3500–2500 (COOH), 2948, 1721, 1626 w (C=O pyridone), 1562, 1475, 1458, 1383, 1311, 1224, 923, 780; δ_H (600 MHz, $CDCl_3$) 4.72 [2H, dt, *J* 6.0, 1.3, NC$\underline{H}_2$CHCH$_2$], 5.29 [1H, dd with further unresolved splitting, *J* 17.3, 0.6, one of NCH$_2$CHC$\underline{H}_2$], 5.40 [1H, dd with further unresolved splitting, *J* 10.2, 0.7, one of

$NCH_2CHC\underline{H}_2$], 5.91–6.03 [1H, m, $NCH_2C\underline{H}CH_2$], 6.58 [1H, dd, *J* 6.9, 6.9, C(5')H], 7.63 [1H, dd, *J* 6.7, 2.2, C(6')H], 8.53 [1H, dd, *J* 7.2, 2.2, C(4')H]; δ_C (150.9 MHz, $CDCl_3$) 52.0 [CH_2, $N\underline{C}H_2CHCH_2$], 108.3 [CH, C(5')H], 118.5 [C, C(3')], 120.5 [CH_2, $NCH_2CH\underline{C}H_2$], 130.7 [CH, $NCH_2\underline{C}HCH_2$], 141.8 [CH, C(6')H], 145.7 [CH, C(4')H], 163.9 [C, C(1)=O or C(2')=O], 165.2 [C, C(1)=O or C(2')=O]. ^{1}H NMR and ^{13}C NMR assignment was aided by HMBC and HSQC 2D NMR experiments (*Appendix V*).

* In retrospect it was discovered that the spectral data assigned by Liu *et al.*[125] corresponds to the *N*-allyl acid **119** and not the *O*-allyl acid **117** as reported and was in excellent agreement with data attributed to **119** in this work.

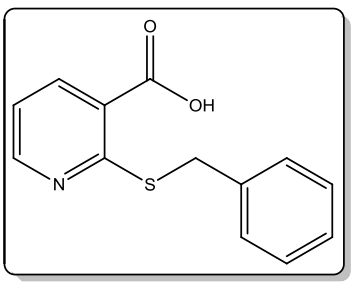
1-Ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid 124[138]



This was prepared following the procedure described for **122**, from a solution of potassium hydroxide (2.86 g, 43.40 mmol) in water/methanol (7:1 ratio, 35/5 mL), 2-hydroxynicotinic acid **118** (3.00 g, 21.56 mmol), ethyl bromide (3.2 mL, 43.4 mmol) and additional potassium hydroxide (1.30 g, 19.7 mmol) to afford the crude N-*ethyl acid* **124** (4.09 g, quantitative yield) as a white solid; m.p. 168–170 °C (lit.,[138] 174 °C); ν_{max}/cm^{-1} (KBr) 3400–2800 (COOH), 2916, 1726, 1630 w, (C=O pyridone), 1568, 1550, 1492, 1449; δ_H (400 MHz, $CDCl_3$) 1.45 [3H, t, *J* 7.2, $NCH_2C\underline{H}_3$], 4.16 [2H, q, *J* 7.2, $NC\underline{H}_2CH_3$], 6.57 [1H, dd, *J* 7.2, 6.8, C(5')H], 7.64 [1H, dd, *J* 6.4, 2.4, C(6')H], 8.51 [1H, dd, *J* 7.2, 2.4, C(4')H], 14.37 [1H, s, $CO_2\underline{H}$]; HRMS (ES+): Exact mass calculated for $C_8H_{10}NO_3$ $[M+H]^+$, 168.0661. Found 168.0655. m/z (ES+) 168.2 $[(M+H)^+$, 100%]. ^{1}H NMR assignment is by analogy with HMBC and HSQC 2D NMR experiments for **119**.

Single crystals of 1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **124** were grown from deuterated chloroform. Crystal data: $C_8H_9NO_3$, M = 167.16, orthorhombic, $P2_12_12_1$, a = 6.9744(15) Å, b = 10.102(2) Å, c = 11.194(2) Å V = 788.7(3) Å^3, Z = 4, D_c = 1.408g cm^{-3}, F_{000} = 352, Mo Kα radiation, λ = 0.7107 Å, T = 296(2) K, $2\theta_{max}$ = 26.52°, μ = 0.109 mm^{-1}, 8921 reflections collected, 1642 unique (R_{int} = 0.0440), final GooF = 1.030, R_1 = 0.0424, wR_2 = 0.0962 (1239 obs. data: $I > 2\sigma(I)$); R_1 = 0.0632, wR_2 = 0.1052 (all data). Full details are given in *Appendix III*.

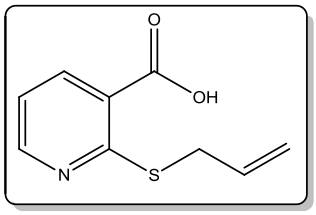
2-(Benzylthio)nicotinic acid 127[127,140]



2-Mercaptonicotinic acid **120** (7.00 g, 45.11 mmol) was added portionwise to a solution of potassium hydroxide (5.06 g, 90.22 mmol) in 2-propanol/water (90/20 mL). Neat benzyl bromide (5.4 mL, 45.11 mmol) was added dropwise to the reaction mixture and the reaction mixture was heated under reflux for 30 min. On cooling, half of the solvent was evaporated; the residue was dissolved in water (50 mL) and acidified with acetic acid (10 mL). The ensuing precipitate was isolated by suction filtration and dried to give the crude *benzylated acid* as a pale yellow solid which was recrystallised from ethanol to give *benzylated acid* **127** (5.33 g, 85%) as pale yellow crystals; m.p. 180–182 °C (lit.,[127,140] 192–194 °C); ν_{max}/cm^{-1} (KBr) 3500–2200 (COOH), 2938, 1678,

1574, 1552, 1423, 1392, 1301, 1070, 710; δ_H (400 MHz, DMSO-d_6) 4.37 [2H, s, SC<u>H</u>$_2$C$_6$H$_5$], 7.22–7.31 [4H, m, 3 × aromatic <u>H</u> and C(5')<u>H</u>], 7.41 [2H, d, *J* 7.2, 2 × aromatic <u>H</u>], 8.21 [1H, dd, *J* 7.6, 1.6, C(4')<u>H</u>], 8.65 [1H, dd, *J* 4.4, 1.6, C(6')<u>H</u>]. Spectral properties were consistent with previously reported data.[127]

2-(Allylthio)nicotinic acid 125

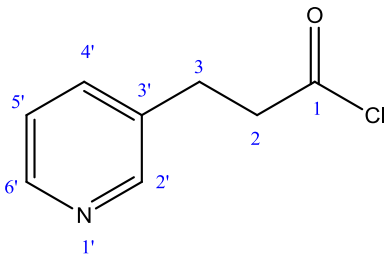


This was prepared following the procedure described for **127**, from a solution of potassium hydroxide (2.47 g, 44.00 mmol) in 2-propanol/water (40/8 mL), 2-mercaptonicotinic acid **120** (3.42 g, 22.00 mmol) and allyl bromide (1.9 mL, 22.00 mmol) to afford the crude *acid* as a pale yellow solid which was recrystallised from ethanol to give pure *acid* **125** (3.00 g, 70%) as white fluffy crystals; m.p. 138–140 °C; ν_{max}/cm^{-1} (KBr) 3300–2400 (COOH), 2920, 1676, 1557, 1390, 1306, 1072, 913, 762; δ_H (400 MHz, $CDCl_3$) 3.89 [2H, d, *J* 6.9, SC<u>H</u>$_2$CHCH$_2$], 5.13 [1H, d with unresolved splitting, *J* 9.9, one of SCH$_2$CHC<u>H</u>$_2$], 5.33 [1H, dd with unresolved splitting, *J* 16.8, 1.5, one of SCH$_2$CHC<u>H</u>$_2$], 5.93–6.10 [1H, m, SCH$_2$C<u>H</u>CH$_2$], 7.10 [1H, dd, *J* 8.1, 4.8, C(5')<u>H</u>], 8.32 [1H, dd, *J* 7.8, 2.1, C(4')<u>H</u>], 8.61 [1H, dd, *J* 4.8, 2.1, C(6')<u>H</u>]; δ_C (75.5 MHz, $CDCl_3$) 33.1 [CH$_2$, S<u>C</u>H$_2$CHCH$_2$], 117.8 [CH$_2$, SCH$_2$CH<u>C</u>H$_2$], 118.4 [CH, <u>C</u>(5')H], 121.9 [C, <u>C</u>(3')], 133.7 [CH, SCH$_2$<u>C</u>HCH$_2$], 139.9 [CH, <u>C</u>(4')H]*, 152.6 [CH, <u>C</u>(6')H]*, 162.7 [C, <u>C</u>(2')SCH$_2$CHCH$_2$], 170.6 [C, <u>C</u>(1)=O]; HRMS (ES+): Exact mass calculated for $C_9H_{10}NO_2S$ $[M+H]^+$, 196.0432. Found 196.0427. m/z (ES+) 196.3 $[(M+H)^+$, 100%].

Single crystals of 2-(allylthio)nicotinic acid **125** were grown from deuterated chloroform. Crystal data: $C_9H_9NO_2S$, M = 195.24, monoclinic, $P2_1/n$, a = 7.7731(16) Å, b = 21.637(6) Å, c = 26.663(8) Å, β = 91.004(7)°, V = 4484.(2) Å^3, Z = 20, D_c = 1.446g cm^{-3}, F_{000} = 2040, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.33°, μ = 0.324 mm^{-1}, 49326 reflections collected, 8967 unique (R_{int} = 0.0595), final GooF = 0.940, R_1 = 0.0364, wR_2 = 0.0842 (6525 obs. data: $I > 2\sigma(I)$); R_1 = 0.0642, wR_2 = 0.0999 (all data). Full details are given in *Appendix III*.

* Assignment of <u>C</u>(4')H and <u>C</u>(6')H in the ^{13}C NMR spectrum was aided by comparison to work by Furdas *et al.* on analogous carboxylic acid **127** and correlates excellently with assignment in that work.[127]

Synthesis of acid chlorides



General numbering scheme for acid chlorides

Characterisation of acid chlorides was carried out using infrared and ^{1}H NMR spectroscopy. It is often not possible to obtain mass spectra and elemental analysis on the acid chlorides due to

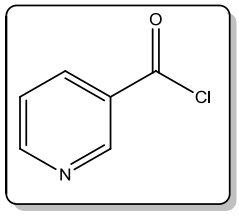
their sensitive nature. In some cases the acid chlorides were characterised solely by infrared spectroscopy.

When the acid chloride was prepared from a commercially available carboxylic acid or purified carboxylic acid, thionyl chloride was used as chlorinating reagent. The acid chlorides which were prepared from crude acids were done so using oxalyl chloride as chlorinating reagent.

A ^{1}H NMR spectrum of the crude product is generally not carried out for the crude acid chlorides with the exception of **160** in this work. ^{1}H NMR analysis was only carried out in general on the acid chlorides purified by vacuum distillation

The acids chlorides are generally stored in the freezer at –20 °C but were always converted to the α-diazoketone within a week of preparation. They can also be stored overnight at room temperature provided they are sealed.

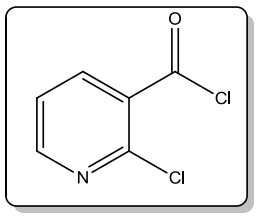
Nicotinoyl chloride 61[32,291]



A mixture of nicotinic acid **12** (10.00 g, 81.23 mmol) in thionyl chloride (59.0 mL, 812 mmol) was heated at 80 °C for 2 h. The reaction mixture was allowed to cool to room temperature followed by removal of the excess thionyl chloride *in vacuo* to give the crude *acid chloride* as a pale yellow solid. To the residue was added pyridine (8.0 mL, 98.68 mmol) and the mixture was purifed by vacuum distillation to give the purified *acid chloride* **61** (5.10 g, 44%)* as a colourless oil; b.p. 45 °C at 0.1 mmHg, (lit.,[32] b.p. 90 °C at 12 mmHg); ν_{max}/cm^{-1} (film) 3121, 1804, 1719, 1635, 1603, 1531, 1467, 1415, 1294, 1235, 1098, 733, 671; δ_H (300 MHz, $CDCl_3$)** 7.64 [1H, dd, *J* 5.1, 3.0, C(5')H], 8.82 [1H, dd, *J* 4.8, 1.5, C(4')H], 9.00 [1H, finely split dt, *J* 8.4, 1.2, C(6')H], 9.05 [1H, d, *J* 1.5, C(2')H]. Preparation of **61** has previously been reported though no assignment of spectral data has been published for this compound.[32] Savonnet and co-workers have included ^{1}H NMR spectrum of **61** in supplementary information, which is in good agreement with data obtained in this work.[291]

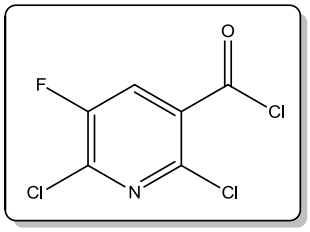
* Sample contains ~46 mol% of unknown side product. Assignment of **61** was aided by comparison with ^{1}H NMR spectrum of **61** published by Savonnet.[291]
** Tentative assignment of ^{1}H NMR signals.

2-Chloronicotinoyl chloride 56[58,59,63]



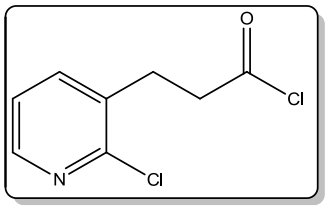
This was prepared following the procedure described for **61**, from 2-chloronicotinic acid **57** (4.00 g, 25.25 mmol), thionyl chloride (18.4 mL, 253 mmol), DMF (2 drops) to provide the crude *acid chloride* as yellow/green oil. Purification by vacuum distillation provided the pure *acid chloride* **56** (4.11 g, 93%) as a colourless oil which readily solidified to a crystalline white solid; b.p. 62 °C at 0.1 mmHg, (lit.,[59] b.p. 98–100 °C at 2 mmHg); m.p. 38 °C; ν_{max}/cm^{-1} (film) 1788, 1558, 1390, 1190; δ_H (300 MHz, $CDCl_3$) 7.47 [1H, dd, *J* 7.8, 4.8, C(5')H], 8.44 [1H, dd, *J* 7.8, 1.8, C(4')H], 8.62 [1H, dd, *J* 4.8, 1.8, C(6')H]. Spectral properties were consistent with previously reported data.[58]

2,6-Dichloro-5-fluoronicotinoyl chloride 59[64]



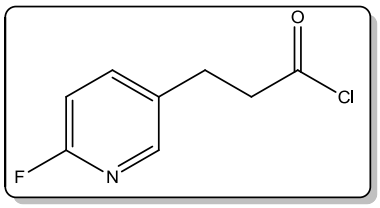
This was prepared following the procedure described for **61**, from thionyl chloride (15.5 mL, 190.5 mmol), 2,6-dichloro-5-fluoronicotinic acid **58** (4.00 g, 19.05 mmol) to yield the crude *acid chloride* as yellow oil. Purification by vacuum distillation gave the *acid chloride* **59** (4.19 g, 96%) as a colourless oil; b.p. 52–55 °C at 0.1 mmHg, (lit.,[64] b.p. 108–110 °C at 4 mmHg); ν_{max}/cm^{-1} (film) 3079, 1775, 1589, 1549, 1404, 1239, 1172, 1128, 1033, 811, 727; δ_H (300 MHz, $CDCl_3$) 8.25 [1H, d, J_{HF} 7.2, C(4')H]. Spectral properties were consistent with previously reported data.[64]

3-(2-Chloropyridin-3-yl)propanoyl chloride 129



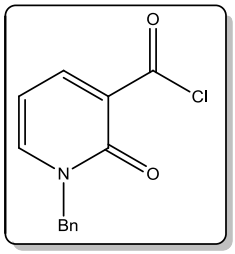
A solution of oxalyl chloride (3.0 mL, 3.82 mmol) in ether (10 mL) was added dropwise to an ethereal solution (40 mL) of 3-(2-chloropyridin-3-yl)propanoic acid **101** (0.64 g, 3.47 mmol) stirring at 0 °C. The temperature was allowed to warm to room temperature and the reaction mixture was stirred for 84 h. The solvent and excess oxalyl chloride were removed under reduced pressure to furnish the crude *acid chloride* **129** (0.70 g, quantitative yield) as a pale yellow solid; ν_{max}/cm^{-1} (KBr) 1791 s, 1736, 1411, 913, 747.

3-(6-Fluoropyridin-3-yl)propanoyl chloride 130



This was prepared following the procedure described for **129**, from a solution of 3-(6-fluoropyridin-3-yl)propanoic acid **115** (1.19 g, 7.00 mmol) in ether (40 mL), oxalyl chloride (6.1 mL, 70.0 mmol) dissolved in ether (10 mL) stirring for 18 h to afford the crude *acid chloride* **130** (0.92 g, 71%) as a viscous yellow oil; ν_{max}/cm^{-1} (KBr) 2937, 1797, 1596, 1487, 1398, 1252.

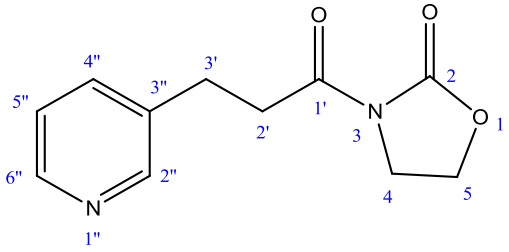
1-Benzyl-2-oxo-1,2-dihydropyridine-3-carbonyl chloride 160[126]



A mixture of 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **122** (5.90 g, 25.74 mmol), distilled toluene (60 mL) and thionyl chloride (18.8 mL, 25.74 mmol) was heated under reflux for 3 h. The excess thionyl chloride and toluene were removed under reduced pressure to afford the crude *acid chloride* **160** (5.75 g, 90%) as a yellow/orange solid; ν_{max}/cm^{-1} (KBr) 3031, 1772 s, 1728, 1655, 1540, 1382, 1222, 956, 765; δ_H (400 MHz, $CDCl_3$) 5.18 [2H, s, $NCH_2C_6H_5$], 6.32 [1H, dd, *J* 6.8, 6.8, C(5')H], 7.29–7.41 [5H, m, 5 × aromatic H]*, 7.71 [1H, d, *J* 4.8, C(6')H], 8.43 [1H, d, *J* 7.2, C(4')H]. Compound **160** has previously been described by Masu and co-workers though no spectral characterisation was carried out on this compound.[126]

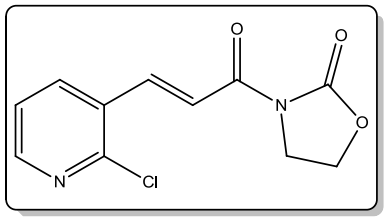
***** Integration is higher than expected.

Preparation of acyloxazolidinones



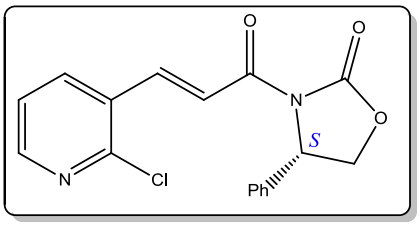
General numbering scheme for acyloxazolidinones

(*E*)-3-[3-(2-Chloropyridin-3-yl)acryloyl]oxazolidin-2-one 89



Thionyl chloride (1.3 mL, 18.36 mmol) was added to a stirring solution of (*E*)-3-(2-chloropyridin-3-yl)acrylic acid **82** (1.25 g, 6.53 mmol) in chloroform (50 mL) and the reaction mixture was heated under reflux for 2 h. The excess solvent and thionyl chloride were removed under reduced pressure by azeotropic distillation to give the crude *acid chloride* **83**. Oxazolidin-2-one **88** (0.37 g, 4.28 mmol) was dissolved in tetrahydrofuran (35 mL) and the mixture cooled to −78 °C. *n*-Butyllithium (1.6 M in hexanes, 2.7 mL, 4.28 mmol) was added dropwise to the oxazolidin-2-one/tetrahydrofuran mixture and the internal temperature was maintained below −70 °C. The crude *acid chloride* was dissolved in tetrahydrofuran (10 mL) and added slowly over 20 min to the reaction mixture. The reaction mixture was stirred for 30 min and the internal temperature maintained below −70 °C; then the reaction was quenched by addition of water (80 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were washed with aqueous saturated sodium bicarbonate (30 mL), brine (20 mL), dried using magnesium sulfate and concentrated under reduced pressure to give the crude *acyloxazolidinone* as a yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (50:50) to (80:20) furnished the pure *acyloxazolidinone* **89** as a white solid (0.55 g, 33%); ν_{max}/cm^{-1} (KBr) 3099, 1769, 1674, 1616, 1575, 1558, 1478, 1384, 1362, 1216, 1202, 1040, 973, 758, 675; δ_H (300 MHz, $CDCl_3$) 4.16 [2H, dd, *J* 8.1, 8.1, NC(4)$\underline{H_2}$], 4.49 [2H, dd, *J* 7.8, 7.8, OC(5)$\underline{H_2}$], 7.31 [1H, dd, *J* 7.8, 4.8, C(5")$\underline{H}$], 7.92 [1H, d, *J* 15.9, C(2')$\underline{H}$], 8.06 [1H, dd, *J* 7.8, 2.1, C(4")$\underline{H}$], 8.17 [1H, d, *J* 15.9, C(3')$\underline{H}$], 8.41 [1H, dd, *J* 4.8, 2.1, C(6")$\underline{H}$]; HRMS (ES+): Exact mass calculated for $C_{11}H_{10}{}^{37}ClN_2O_3$ $[M+H]^+$, 255.0350. Found 255.0343 and exact mass calculated for $C_{11}H_{10}{}^{35}ClN_2O_3$ $[M+H]^+$, 253.0380. Found 253.0373. m/z 255.0 {$[(C_{11}H_{10}{}^{37}ClN_2O_3)^+]$, 34%}, 253.0 {$[(C_{11}H_{10}{}^{35}ClN_2O_3)^+]$, 100%}.

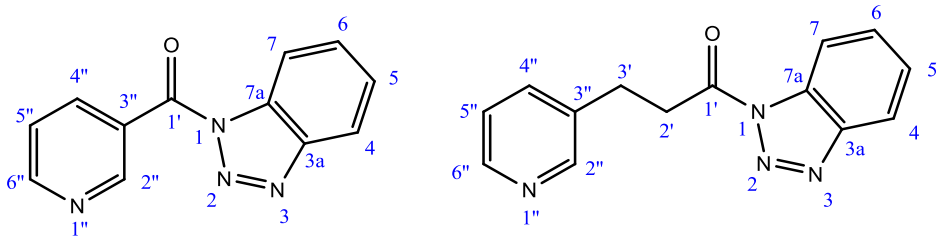
(4*S*,2*E*)-3-[3-(2-Chloropyridin-3-yl)acryloyl]-4-phenyloxazolidin-2-one 84[41]



This was prepared following the procedure described for **89**, from acid **82** (1.00 g, 5.44 mmol), thionyl chloride (1.1 mL, 18.36 mmol) and chloroform (50 mL) to prepare the crude *acid chloride* **83**. *n*-Butyllithium (1.6 M in hexanes, 2.8 mL, 4.28 mmol) was added dropwise to a solution of (*S*)-(+)-4-phenyl-2-oxazolidinone **87** (0.59 g, 3.62 mmol) in tetrahydrofuran (35 mL). A tetrahydrofuran solution (10 mL) of the crude *acid chloride* was added dropwise to the reaction mixture to give the crude *acyloxazolidinone* as a yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (50:50) to (80:20) afforded the pure *acyloxazolidinone* **84** as a white solid (0.65 g, 37%); ν_{max}/cm^{-1} (KBr) 2977, 1776, 1687, 1620, 1402, 1387, 1340, 1119, 1071, 732, 680; δ_H (300 MHz, $CDCl_3$)* 4.33 [1H, dd, *J* 9.0, 3.9, one of OC(5)$\underline{H}_2$], 4.76 [1H, dd, *J* 9.0, 8.7, C(4)$\underline{H}C_6H_5$], 5.56 [1H, dd, *J* 8.7, 3.9, one of OC(5)$\underline{H}_2$], 7.25–7.46 [6H, m, C(5")$\underline{H}$ and 5 × aromatic $\underline{H}$], 7.94 [1H, d, *J* 15.6, C(2')$\underline{H}$], 8.02–8.09 [2H, m consisting of overlapping d and dd, C(3)$\underline{H}$ and C(4")$\underline{H}$], 8.37 [1H, dd, *J* 4.8, 1.8, C(6")$\underline{H}$]. ^{1}H NMR spectral properties were consistent with previously reported data,[41] while infrared analysis for **84** was not previously reported in the literature.

* Sample contains ethyl acetate.

Synthesis of acylbenzotriazoles



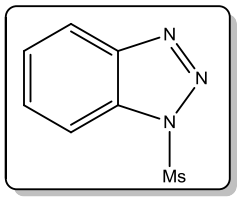
Numbering scheme for acylbenzotriazoles

In the preparation of the *N*-acylbenzotriazoles, the samples often contained an inseparable component identified as 1*H*-benzotriazole **175**. The samples were brought forward without further purification and the presence of this impurity had no effect on subsequent transformations. The usual procedure to eliminate excess 1*H*-benzotriazole **175** involves washing with aqueous acid but this could not be carried out here due to the susceptibility of the pyridine ring to protonation by acid.

The structural assignment for the short-chain acylbenzotriazoles follows that described by Katritzky,[56] while assignment for the long-chain acylbenzotriazoles was aided from 2D NMR HSQC and HMBC experiments for 3-(pyridin-3-yl)propanoic acid **47** (*Appendix IV*), as well as predicted signals described for **47** by Griffiths.[50]

The Methods A–C used to prepare the acylbenzotriazoles relate to earlier discussion (**Section 2.3.2.2**).

1-(Methylsulfonyl)-1*H*-benzo[d][1,2,3]triazole (BtMs) 176[56,292]

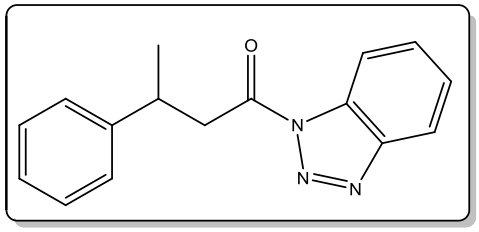


A solution of mesyl chloride (9.3 mL, 120 mmol) in distilled toluene (30 mL) was added dropwise to an ice-cold solution of 1*H*-benzotriazole **175** (11.90 g, 100 mmol) and pyridine (12.2 mL, 160 mmol). The reaction mixture was stirred overnight at room temperature, diluted with ethyl acetate (100 mL) and washed with water (40 mL) to separate the organic layer. The organic layer was washed successively with water (20 mL), brine (20 mL), dried with magnesium sulfate and concentrated *in vacuo* to afford the crude product as an off-white solid. The crude product was recrystallised from hot benzene to give the pure *mesylated benzotriazole* (BtMs) **176** as a fluffy white solid (20.60 g, quantitative yield)*; m.p. 108–110 °C (lit.,[292] 110–111.5 °C); ν_{max}/cm^{-1} (KBr) 3027, 1609, 1590, 1384, 1183, 946, 768, 750; δ_H (400 MHz, $CDCl_3$) 3.51 [3H, s, SO_2CH_3], 7.55 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 7.69 [1H, ddd, *J* 8.4, 6.8, 0.8, C(5)H or C(6)H], 8.03 [1H, dt, *J* 8.4, 2.0, C(4)H or C(7)H], 8.17 [1H, dt, *J* 8.4, 2.0, C(4)H or C(7)H]. Spectral properties were in agreement with reported data.[292]

* In general the material was clean enough to use without recrystallisation.

Method C: One-pot procedure from acid[196]

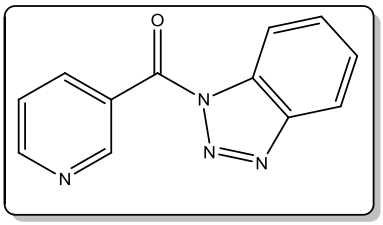
1-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-3-phenylbutan-1-one 178[167]



To a solution of 1*H*-benzotriazole **175** (5.80 g, 48.72 mmol) in dichloromethane (50 mL) was added thionyl chloride (0.9 mL, 12.18 mmol) in one portion and the reaction mixture stirred for 30 min at room temperature. 3-Phenylbutanoic acid **177** (2.00 g, 12.18 mmol) was added in one portion and a colour change from bright yellow to pale milky white was observed upon addition. The reaction mixture was stirred for a further 2 h at room temperature. The white precipitate was filtered off and extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with aqueous sodium hydroxide (1.0 M, 3 × 60 mL), dried with magnesium sulfate and concentrated under reduced pressure to yield the crude *acylbenzotriazole* as a pale yellow oil which readily solidified. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) afforded the pure *acylbenzotriazole* **178** (2.68 g, 88%) as a white solid; m.p. 62–64 °C; ν_{max}/cm^{-1} (KBr) 2964, 1735, 1708, 1486, 1451, 1376, 1289, 1211, 1168, 979, 749, 700; δ_H (300 MHz, $CDCl_3$) 1.45 [3H, d, *J* 6.8, CHC(4')H_3], 3.60–3.69 [2H, m, one of C(2')H_2 and C(3')HCH$_3$], 3.76–3.85 [1H, m, one of C(2')H_2], 7.18–7.22 [1H, m, aromatic H], 7.28–7.35 [4H, m, 4 × aromatic H], 7.48 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 7.61 [1H, ddd, *J* 8.0, 7.2, 1.2, C(5)H or C(6)H], 8.09 [1H, d with further unresolved splitting, *J* 8.0, C(4)H or C(7)H], 8.24 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H]; δ_C (75.5 MHz, $CDCl_3$) 22.1 [CH_3, C(4')H_3], 36.1 [CH, C(3')H], 43.6 [CH_2, C(2')H_2], 114.5 [CH, C(7)H], 120.1 [CH, C(4)H], 126.1 [CH, one of aromatic CH, C(5)H or C(6)H], 126.7 [CH, one of aromatic CH, C(5)H or C(6)H], 126.8 [CH, 2 × aromatic CH], 128.6 [CH, 2 × aromatic CH], 130.4 [CH, C(5)H or C(6)H], 131.1 [C, C(7)a], 145.1 and 146.1 [2 × C, C(3)a and aromatic C], 171.1 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{16}H_{16}N_3O$ $[M+H]^+$, 266.1293. Found 266.1292. m/z (ES+) 266.4 $[(M+H)^+$, 12%].

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(pyridin-3-yl)methanone 179[56]

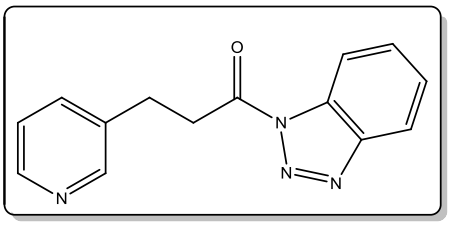
Method B: From BtMs **176** *and acid*[56]



A mixture of nicotinic acid **12** (3.12 g, 24.37 mmol), BtMs **176** (4.81 g, 24.37 mmol) and triethylamine (4.8 mL, 34.11 mmol) in tetrahydrofuran (60 mL) was heated under reflux overnight. After 18 h, the solvent was evaporated and the residue was diluted in dichloromethane (100 mL), washed with brine (30 mL), dried with magnesium sulfate and concentrated under reduced pressure to furnish the crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *acylbenzotriazole* **179** as a white solid (4.12 g, 75%)*; m.p. 87–89 °C (lit.,[56] 86–89 °C); ν_{max}/cm^{-1} (KBr) 2959, 1718, 1624, 1596, 1418, 1323, 1300, 1210, 741; δ_H (400 MHz, $CDCl_3$) 7.53–7.61 [2H, m, C(5)H or C(6)H and C(5")H], 7.75 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 8.19 [1H, d, *J* 8.4, C(4)H or C(7)H], 8.42 [1H, d, *J* 8.4, C(4)H or C(7)H], 8.56 [1H, dt, *J* 8.0, 1.6, C(4")H], 8.90 [1H, dd, *J* 4.8, 1.6, C(6")H], 9.43 [1H, dd, *J* 2.0, 0.4, C(2")H]. ^{1}H NMR spectral properties were consistent with reported data.[56]

* Sample contains ~8 mol% 1*H*-benzotriazole **175**.

1-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-3-(pyridin-3-yl)propan-1-one 180

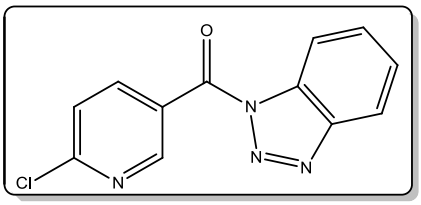


This was prepared following the procedure described for **178** (Method B: From BtMS **176** and acid), from a commercial sample of 3-pyridinepropanoic acid **47** (2.50 g, 16.54 mmol), triethylamine (4.8 mL, 34.11 mmol), BtMs **176** (3.26 g, 16.54 mmol) and tetrahydrofuran (60 mL) to give the crude *acylbenzotriazole.* Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *acylbenzotriazole* **180** as a white solid (2.23 g, 54%)*; m.p. 82–84 °C; ν_{max}/cm^{-1} (KBr) 2928, 1736, 1396, 1206, 967, 746; δ_H (400 MHz, $CDCl_3$) 3.25 [2H, t, *J* 7.2, C(2')H_2], 3.79 [2H, t, *J* 7.6, C(3')H_2], 7.26 [1H, dd, *J* 4.8, 3.2, C(5")H], 7.50 [1H, t, *J* 7.6, C(5)H or C(6)H], 7.63–7.68 [2H, m, C(4")H and C(5)H or C(6)H], 8.11 [1H, d, *J* 8.4, C(4)H or C(7)H], 8.27 [1H, d, *J* 8.0, C(4)H or C(7)H], 8.49 [1H, dd, *J* 4.8, 1.6, C(6")H], 8.61 [1H, d, *J* 2.0, C(2")H]; δ_C (75.5 MHz, $CDCl_3$) 27.3 [CH_2, C(3')H_2], 36.6 [CH_2, C(2')H_2], 114.3 [CH, C(7)H], 120.2 [CH, C(4)H], 123.5 [CH, C(5")H], 126.3 [CH, C(5)H or C(6)H], 130.5 [CH, C(5)H or C(6)H], 131.0 [C, C(7)a], 135.3 [C, C(3")], 136.1 [CH, C(4")H], 146.2 [C, C(3)a], 148.0 [CH, C(6")H], 149.9 [CH, C(2")H], 171.0 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{14}H_{13}N_4O$ $[M+H]^+$, 253.1089. Found 253.1098. m/z (ES+) 253.0 $[(M+H)^+$, 100%].

* Sample contains ~16 mol% 1*H*-benzotriazole **175** as well as residual ethyl acetate.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(6-chloropyridin-3-yl)methanone 182

Method A: From acid chloride[167]



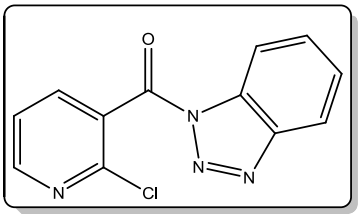
The commercial 6-chloronicotinoyl chloride **60** (3.00 g, 17.05 mmol) was dissolved in dichloromethane (40 mL) and the solution was stirred at 0 °C. 1*H*-Benzotriazole **175** (2.03 g, 17.05 mmol) was added portionwise to the reaction mixture followed by addition of diisopropylethylamine (3.3 mL, 18.74 mmol) in one portion. The reaction mixture was stirred for 1 h at 0 °C and a milky suspension was observed. The reaction mixture was warmed to room temperature and stirred for a further 4 h. The reaction mixture was washed with aqueous hydrochloric acid (3.2 M, 20 mL) and stirred vigorously for 5 min. Separation of the organic layer was followed by extraction with dichloromethane (1 × 20 mL). The combined organic extracts were washed with aqueous hydrochloric acid (3.2 M, 20 mL), brine (20 mL), dried with magnesium sulfate and concentrated to give the crude *acylbenzotriazole* **182** as an off-white solid (3.89 g, 88%); m.p. 128–130 °C; ν_{max}/cm^{-1} (KBr) 3052, 1702, 1578, 1560, 1484, 1452, 1399, 1289, 1062, 756; δ_H (400 MHz, $CDCl_3$) 7.55–7.62 [2H, m overlapping dd and ddd, C(5")H and C(5)H or C(6)H], 7.75 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 8.20 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H], 8.40 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H], 8.56 [1H, dd, *J* 8.4, 2.4, C(4")H], 9.25 [1H, d, *J* 2.4, C(6")H]; δ_C (75.5 MHz, $CDCl_3$) 114.7 [CH, C(7)H], 120.5 [CH, C(4)H], 124.1 [CH, C(5")H], 126.6 [C, C(3")], 126.9 [C, C(5)H or C(6)H], 130.1 [CH, C(5)H or C(6)H], 131.9 [C, C(7)a], 141.5 [CH, C(4")H], 145.8 [C, C(3)a], 152.7 [CH, C(2")H], 156.3 [C, C(6")Cl], 164.0 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{12}H_8{}^{35}ClN_4O$ $[M+H]^+$, 259.0387. Found 259.0392. m/z (ES+) 261.2 {[$(C_{12}H_8{}^{37}ClN_4O)^+$], 16%}, 259.1 {[$(C_{12}H_8{}^{35}ClN_4O)^+$], 30%}.

Method C: One-pot procedure from acid

This was prepared following the procedure described for **178** (Method C: One-pot procedure from acid), from a solution of 1*H*-benzotriazole **175** (15.12 g, 127 mmol) in dichloromethane (50 mL), thionyl chloride (2.3 mL, 31.74 mmol) and 6-chloronicotinic acid (5.00 g, 31.74 mmol) to yield the crude *acylbenzotriazole* as a pale yellow oil which readily solidified. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) afforded the purified *acylbenzotriazole* **182** (7.72 g, 92%) as a white solid which contained an appreciable amount of 1*H*-benzotriazole **175**. This was followed by repeated chromatograpy using ethyl acetate/hexane (10:90) to (20:80) to (40:60) to furnish the pure *acylbenzotriazole* **182** (0.91 g, 11%) was a white solid with spectral data identical to that reported above.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(2-chloropyridin-3-yl)methanone 183

Method C: One-pot preparation from acid



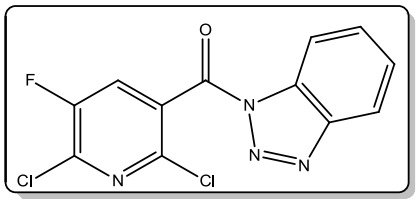
This was prepared following the procedure described for **178** (Method C: One-pot procedure from acid), from a solution of 1*H*-benzotriazole **175** (15.12 g, 127 mmol) in dichloromethane (60 mL), thionyl chloride (2.3 mL, 31.74 mmol) and 2-chloronicotinic acid **57** (5.00 g, 31.74 mmol) to furnish the

crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (30:70) to (40:60) provided the pure *acylbenzotriazole* **183** as a white solid (4.59 g, 56%); m.p. 118–119 °C; ν_{max}/cm^{-1} (KBr) 3112, 1724, 1583, 1561, 1486, 1452, 1394, 1152, 1058, 938, 755; δ_H (300 MHz, $CDCl_3$) 7.47 [1H, dd, *J* 7.8, 5.1, C(5")H], 7.61 [1H, ddd, *J* 8.1, 7.2, 1.2, C(5)H or C(6)H], 7.77 [1H, ddd, *J* 8.1, 7.2, 1.2, C(5)H or C(6)H], 8.01 [1H, dd, *J* 7.5, 1.8 C(4")H], 8.19 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H], 8.42 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H], 8.65 [1H, dd, *J* 4.8, 1.8, C(6")H]; δ_C (150.9 MHz, $CDCl_3$) 114.4 [CH, C(7)H], 120.6 [CH, C(4)H], 122.0 [CH, C(5")H], 127.0 [CH, C(5)H or C(6)H], 129.7 [C, C(3") or C(7)a], 131.07 [CH, C(5)H or C(6)H], 131.14 [C, C(3") or C(7)a], 138.9 [CH, C(4")H], 146.4 [C, C(3)a], 148.6 [C, C(2")Cl], 152.0 [CH, C(6")H], 164.3 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{12}H_8{}^{35}ClN_4O$ $[M+H]^+$, 259.0387. Found 259.0382. m/z (ES+) 261.1 {$[(C_{12}H_8{}^{37}ClN_4O)^+]$, 34%}, 259.20 {$[(C_{12}H_8{}^{35}ClN_4O)^+]$, 98%}.

Method A: From acid chloride

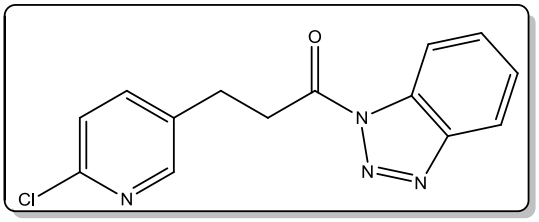
This was prepared following the procedure described for **181** (Method A: From acid chloride), from a solution of acid chloride **56** (5.78 g, 32.85 mmol) in doubly distilled dichloromethane (60 mL), 1*H*-benzotriazole **175** (3.91 g, 32.85 mmol) and diisopropylethylamine (2.7 mL, 36.14 mmol) to give the crude *acylbenzotriazole* **183** as an off-white solid (7.36 g, 87%). Spectral characteristics were identical to those obtained above.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)(2,6-dichloro-5-fluoropyridin-3-yl)methanone 184



This was prepared following the procedure described for **178** (Method C: One-pot preparation from acid), from a solution of 1*H*-benzotrizole **175** (6.02 g, 50.52 mmol) in dichloromethane (50 mL), thionyl chloride (0.9 mL, 12.63 mmol) and 2,6-dichloro-5-fluoronicotinic acid **58** (2.65 g, 12.63 mmol) to generate the crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (30:70) provided the pure *acylbenzotriazole* **184** (3.54 g, 90%) as a white solid; (Found C, 54.84; H, 3.04; N, 13.31; $C_{14}H_8Cl_2FN_3$. Requires C, 54.57; H, 2.62; N, 13.64%); m.p. 118–120 °C; ν_{max}/cm^{-1} (KBr) 3064, 1723, 1594, 1558, 1484, 1452, 1410, 1021, 850; δ_H (400 MHz, $CDCl_3$) 7.63 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 7.79 [1H, ddd, *J* 9.2, 7.2, 1.2, C(5)H or C(6)H], 7.82 [1H, d, J_{HF} 6.8, C(4")H], 8.20 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H], 8.40 [1H, d with further unresolved splitting, *J* 8.4, C(4)H or C(7)H]; δ_C (75.5 MHz, $CDCl_3$) 114.3 [CH, C(7)H], 120.7 [CH, C(4)H], 127.26 [CH, d, $^2J_{CF}$ 22.9, C(4")H], 127.32 [CH, C(5)H or C(6)H], 129.2 [C, d, $^3J_{CF}$ 2.6, C(3")], 131.0 [C, C(7)a], 131.3 [CH, C(5)H or C(6)H], 140.8 [C, d, $^2J_{CF}$ 20.8, C(6")Cl], 142.1 [C, d, $^4J_{CF}$ 3.9, C(2")Cl], 146.4 [C, C(3)a], 153.6 [C, d, $^1J_{CF}$ 263.9, C(5")F], 161.9 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{12}H_6{}^{35}Cl_2FN_4O$ $[M+H]^+$, 310.9903. Found 310.9918. m/z (ES+) 311.1{$[(C_{12}H_6{}^{35}Cl_2FN_4O)^+]$, 18%}.

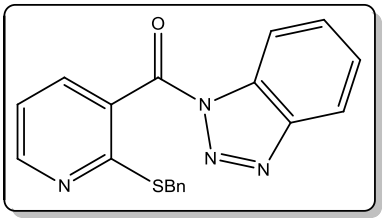
1-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-3-(6-chloropyridin-3-yl)propan-1-one 185



This was prepared following the procedure described for **178** (Method C: One-pot preparation from acid), from a solution of 1*H*-benzotriazole **175** (9.00 g, 75.42 mmol) in dichloromethane (50 mL), thionyl chloride (1.4 mL, 18.86 mmol) and 3-(6-chloropyridin-3-yl)propanoic acid **102** (3.50 g, 18.86 mmol) to furnish the crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (25:80) to (30:70) gave the pure *acylbenzotriazole* **185** (3.52 g, 65%) as a white solid; m.p. 99–100 °C; (Found C, 58.51; H, 3.85; N, 19.44. $C_{14}H_{12}ClN_4O$ requires C, 58.65; H, 3.87; N, 19.04%); ν_{max}/cm^{-1} (KBr) 1742, 1700, 1568, 1458, 1444, 1374, 1289, 1102, 961, 786, 775, 754; δ_H (300 MHz, $CDCl_3$) 3.24 [2H, t, *J* 7.5, C(2')$\underline{H}_2$], 3.78 [2H, t, *J* 7.5, C(3')$\underline{H}_2$], 7.28 [1H, d, *J* 9.0, C(5")$\underline{H}$], 7.52 [1H, ddd, *J* 8.1, 7.2, 0.9, C(5)$\underline{H}$ or C(6)$\underline{H}$], 7.63–7.70 [2H, m, C(5)$\underline{H}$ or C(6)$\underline{H}$ and C(4")$\underline{H}$], 8.12 [1H, d with further unresolved splitting, *J* 8.4, C(4)$\underline{H}$ or C(7)$\underline{H}$], 8.26 [1H, d with further unresolved splitting, *J* 8.4, C(4)$\underline{H}$ or C(7)$\underline{H}$], 8.38 [1H, d, *J* 2.4, C(2")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 26.5 [CH_2, $\underline{C}$(3')H_2], 36.4 [CH_2, $\underline{C}$(2')H_2], 114.3 [CH, $\underline{C}$(7)H], 120.3 [CH, $\underline{C}$(4)H], 124.1 [CH, $\underline{C}$(5")H], 126.3 [CH, $\underline{C}$(5)H or $\underline{C}$(6)H], 130.6 [CH, $\underline{C}$(5)H or $\underline{C}$(6)H], 130.9 [C, $\underline{C}$(7)a], 134.2 [C, $\underline{C}$(3")], 138.9 [CH, $\underline{C}$(4")H], 146.2 [C, $\underline{C}$(3)a], 149.77 [CH, $\underline{C}$(2")H], 149.82 [C, $\underline{C}$(6")Cl], 170.8 [C, $\underline{C}$(1')=O]; HRMS (ES+): Exact mass calculated for $C_{14}H_{12}{}^{35}ClN_4O$ $[M+H]^+$, 287.0700. Found 287.0692. m/z (ES+) 289.3 {[$(C_{14}H_{12}{}^{37}ClN_4O)^+$], 32%}, 287.3 {[$(C_{14}H_{12}{}^{35}ClN_4O)^+$], 100%}.

Single crystals of 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-(6-chloropyridin-3-yl)propan-1-one **185** were grown from deuterated chloroform. Crystal data: $C_{14}H_{11}ClN_4O$, M = 286.72, monoclinic, $P2_1/c$, a = 7.445(6) Å, b = 13.049(10) Å, c = 13.882(11) Å, β = 104.051(18), V = 1308.3(18) $Å^3$, Z = 4, D_c = 1.456 g cm^{-3}, F_{000} = 592, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.67°, μ = 0.293 mm^{-1}, 12116 reflections collected, 2690 unique (R_{int} = 0.0546), final GooF = 1.077, R_1 = 0.0456, wR_2 = 0.1191 (1912 obs. data: $I > 2\sigma(I)$); R_1 = 0.0708, wR_2 = 0.1382 (all data). Full details are given in *Appendix III*.

(1*H*-Benzo[d][1,2,3]triazol-1-yl)[2-(benzylthio)pyridin-3-yl]methanone 186

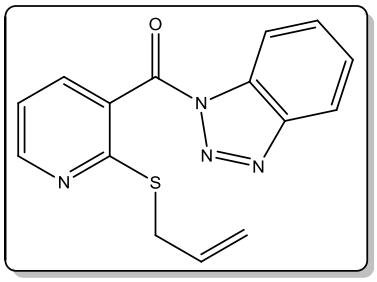


This was prepared following the procedure described for **178** (Method C: One-pot preparation from acid), from a solution of 1*H*-benzotriazole **175** (5.31 g, 44.60) in dichloromethane (50 mL), thionyl chloride (0.8 mL, 11.15 mmol) and the carboxylic acid **127** (2.74 g, 11.15 mmol) to furnish the crude *acylbenzotriazole*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) gave the pure *acylbenzotriazole* **186** (0.64 g, 18%) as a white solid; m.p. 74–76 °C; ν_{max}/cm^{-1} (KBr) 3062, 1686, 1573, 1542, 1448, 1390, 1349, 1319, 1285, 1141, 1045, 931, 884, 755; δ_H (400 MHz, $CDCl_3$) 4.51 [2H, s, S$\underline{C}H_2C_6H_5$], 7.18–7.30 [4H, m, 3 × aromatic $\underline{H}$ and C(5")$\underline{H}$]*, 7.35–7.40 [2H, m, 2 × aromatic $\underline{H}$], 7.54–7.60 [1H, m, C(5)$\underline{H}$ or C(6)$\underline{H}$], 7.69–7.73 [1H, m, C(5)$\underline{H}$ or C(6)$\underline{H}$], 8.12 [1H, dd, *J* 7.6, 1.6, C(4")$\underline{H}$], 8.15 [1H, br d, *J* 8.0, C(4)$\underline{H}$ or C(7)$\underline{H}$], 8.38 [1H, br d, 8.4, C(4)$\underline{H}$ or C(7)$\underline{H}$], 8.69 [1H, dd, *J* 4.8, 1.6, C(6")$\underline{H}$]; δ_C (150.9 MHz, $CDCl_3$) 35.2 [CH_2, S$\underline{C}H_2C_6H_5$], 114.8 [CH, $\underline{C}$(7)H], 118.4 [CH, $\underline{C}$(4)H], 120.3 [CH, $\underline{C}$(5")H], 125.7 [C, $\underline{C}$(3")], 126.7 [CH,

C(5)H or C(6)H], 127.2 [CH, aromatic CH], 128.4 [CH, 2 × aromatic CH], 129.3 [CH, 2 × aromatic CH], 130.7 [CH, C(5)H or C(6)H], 131.7 [C, C(7)a], 137.1 [C, aromatic C], 139.3 [CH, C(4")H], 146.0 [C, C(3)a], 151.9 [CH, C(6")H], 160.6 [C, C(2")$SCH_2C_6H_5$], 165.2 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{19}H_{15}N_4OS$ $[M+H]^+$, 347.0967. Found 347.0955. m/z (ES+) 347.2 $[(M+H)^+$, 100%].

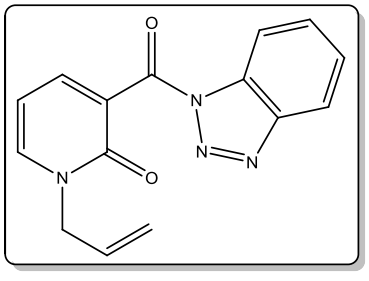
* Integration is high due to overlap with $CDCl_3$.

[2-(Allylthio)pyridin-3-yl](1*H*-benzo[d][1,2,3]triazol-1-yl)methanone 187



This was prepared following the procedure described for **178** (Method C: One-pot preparation from acid), from a solution of 1*H*-benzotriazole **175** (7.32 g, 61.46 mmol) in dichloromethane (50 mL), thionyl chloride (1.1 mL, 15.37 mmol) and carboxylic acid **125** (3.00 g, 15.37 mmol) to give the crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (15:85) to (20:80) afforded the pure *acylbenzotriazole* **187** (0.91 g, 20%) as a white solid; m.p. 109–110 °C; ν_{max}/cm^{-1} (KBr) 3078, 1718, 1710, 1577, 1552, 1486, 1448, 1400, 1362, 1288, 1046, 935, 749; δ_H (400 MHz, $CDCl_3$) 3.93 [2H, d, *J* 6.8, SCH_2CHCH_2], 5.09 [1H, d with further unresolved splitting, *J* 10.0, one of SCH_2CHCH_2], 5.27 [1H, d with further unresolved splitting, *J* 17.2, one of SCH_2CHCH_2], 5.88–5.98 [1H, m, SCH_2CHCH_2], 7.20 [1H, dd, *J* 8.0, 5.2, C(5")H], 7.57 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 7.73 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 8.09 [1H, dd, *J* 7.6, 1.6, C(4")H], 8.17 [1H, d, *J* 8.4, C(4)H or C(7)H], 8.41 [1H, d, *J* 8.4, C(4)H or C(7)H], 8.66 [1H, dd, *J* 5.2, 2.0, C(6")H]; δ_C (150.9 MHz, $CDCl_3$) 33.5 [CH_2, SCH_2CHCH_2], 114.7 [CH, C(7)H], 118.1 [CH_2, SCH_2CHCH_2], 118.4 [CH, C(4)H], 120.3 [CH, C(5")H], 126.2 [C, C(3")], 126.7 [CH, C(5)H or C(6)H], 130.8 [CH, C(5)H or C(6)H], 131.7 [C, C(7)a], 133.3 [CH, SCH_2CHCH_2], 139.2 [CH, C(4")H], 146.1 [C, C(3)a], 151.8 [CH, C(6")H], 160.1 [C, C(2")SCH_2CHCH_2], 165.3 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{15}H_{13}N_4OS$ $[M+H]^+$, 297.0810. Found 297.0799. m/z (ES+) 297.2 $[(M+H)^+$, 100%].

1-Allyl-3-(1*H*-benzo[d][1,2,3]triazole-1-carbonyl)pyridin-2(1*H*)-one 188



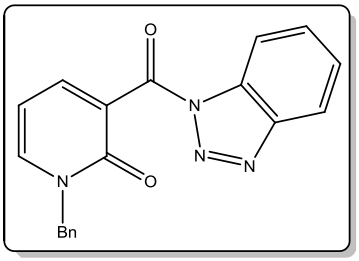
This was prepared following the procedure described for **179** (Method B: From BtMS **176** and acid), from a solution of BtMs **176** (4.40 g, 22.32 mmol), carboxylic acid **119** (4.00 g, 22.32 mmol) in tetrahydrofuran (80 mL) and triethylamine (4.4 mL, 31.25 mmol) to give the crude *acylbenzotriazole* as a burgundy-coloured solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) to (40:60) to (50:50) afforded the purified *acylbenzotriazole* **188** (0.92 g, 15%)* as a pale yellow oil which later solidified to off-white solid; ν_{max}/cm^{-1} (KBr) 1719, 1624, 1560, 1475, 1458, 1420, 1382, 1310, 1224, 1209, 780, 740; δ_H (400 MHz, $CDCl_3$) 4.64 [2H, dt, *J* 6.0, 1.2, NCH_2CHCH_2], 5.30 [1H, dd, *J* 15.6, 1.2, one of NCH_2CHCH_2], 5.33 [1H, dd, *J* 8.8, 1.2, one of NCH_2CHCH_2], 5.91–6.04 [1H, m,

$NCH_2C\underline{H}CH_2$], 6.38 [1H, dd, *J* 7.2, 7.2, C(5")H], 7.54 [1H, ddd, *J* 8.4, 7.2, 0.8, C(5)H or C(6)H], 7.58 [1H, dd, *J* 6.8, 2.0, C(4")H or C(6")H], 7.67 [1H, ddd, *J* 8.0, 7.2, 0.8, C(5)H or C(6)H], 7.90 [1H, dd, *J* 6.8, 2.0, C(4")H or C(6")H], 8.10 [1H, br d, 8.0, C(4)H or C(7)H], 8.32 [1H, br d, *J* 8.0, C(4)H or C(7)H,]; δ_C (125.8 MHz, $CDCl_3$) 51.6 [CH_2, $N\underline{C}H_2CHCH_2$], 105.2 [CH, C(7)H], 114.2 [CH, C(5")H], 119.6 [CH_2, $NCH_2CH\underline{C}H_2$], 120.0 [CH, C(4)H], 124.7 [C, C(3")], 126.2 [CH, C(5)H or C(6)H], 130.6 [CH, C(5)H or C(6)H], 131.2 [C, C(7)a], 131.5 [CH, $NCH_2\underline{C}HCH_2$], 141.5 [CH, C(4")H or C(6")H], 142.8 [CH, C(4")H or C(6")H], 147.0 [C, C(3)a], 159.2 [C, C(2")=O], 164.8 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{15}H_{13}N_4O_2$ $[M+H]^+$, 281.1039. Found 281.1034. m/z (ES+) 281.2 $[(M+H)^+$, 98%], 253.3 {$[(M+H)–N_2$ or $CO]^+$, 100%}.

* Sample contains ~14 mol% 1*H*-benzotriazole **175** and ~8 mol% acid **119**.

3-(1*H*-Benzo[d][1,2,3]triazole-1-carbonyl)-1-benzylpyridin-2(1*H*)-one 189

Method C: One-pot preparation from acid



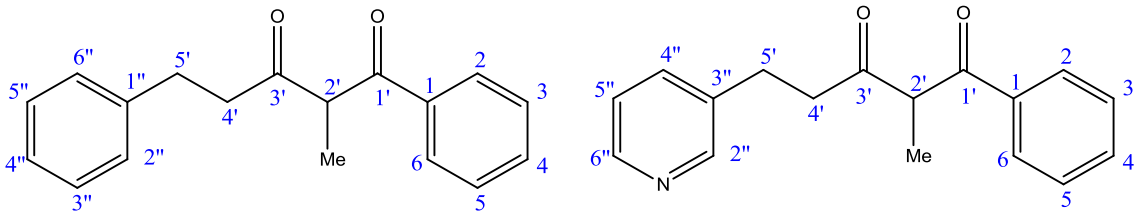
This was prepared following the procedure described for **178** (Method C: One-pot preparation from acid), from a solution of 1*H*-benzotriazole **175** (6.60 g, 55.39 mmol) in dichloromethane (60 mL), thionyl chloride (1.0 mL, 13.85 mmol) and carboxylic acid **122** (3.17 g, 11.15 mmol) to furnish the crude *acylbenzotriazole* as a white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) to (80:20) afforded the pure *acylbenzotriazole* **189** (0.65 g, 13%) as a white solid; m.p. 165–167 °C; ν_{max}/cm^{-1} (KBr) 3036, 1735, 1720, 1630, 1560, 1478, 1457, 1435, 1210, 779, 699; δ_H (400 MHz, $CDCl_3$) 5.22 [2H, s, $NC\underline{H}_2C_6H_5$], 6.36 [1H, dd, *J* 6.8, 6.8, C(5")H], 7.30–7.42 [5H, m, 5 × aromatic H], 7.52 [1H, ddd, *J* 9.2, 8.0, 0.8, C(5)H or C(6)H], 7.58 [1H, dd, *J* 6.8, 2.0, C(4")H], 7.68 [1H, ddd, *J* 8.0, 6.8, 2.0, C(5)H or C(6)H], 7.90 [1H, dd, *J* 7.2, 2.0, C(6")H], 8.13 [1H, br d, *J* 8.4, C(4)H or C(7)H], 8.34 [1H, br d, *J* 8.4, C(4)H or C(7)H]; δ_C (75.5 MHz, $CDCl_3$) 52.6 [CH_2, $N\underline{C}H_2C_6H_5$], 105.3 [CH, C(5")H], 114.4 [CH, C(7)H], 120.1 [CH, C(4)H], 125.0 [C, C(3")], 126.2 [CH, C(5)H or C(6)H], 128.5 [CH, aromatic CH], 128.5 [CH, 2 × aromatic CH], 129.1 [CH, 2 × aromatic CH], 130.3 [CH, C(5)H or C(6)H], 131.3 [C, C(7)a], 135.4 [C, aromatic C], 141.6 [CH, C(4")H or C(6")H], 142.8 [CH, C(4")H or C(6")H], 146.1 [C, C(3)a], 152.2 [C, C(2")=O], 159.5 [C, C(1')=O]; HRMS (ES+): Exact mass calculated for $C_{19}H_{15}N_4O_2$ $[M+H]^+$, 331.1195. Found 331.1191. m/z (ES+) 331.3 $[(M+H)^+$, 92%], 303.3 {$[(M+H)–N_2$ or $CO]^+$, 100%}.

Single crystals of 3-(1*H*-benzo[d][1,2,3]triazole-1-carbonyl)-1-benzylpyridin-2(1*H*)-one **189** were grown from deuterated chloroform. Crystal data: $C_{19}H_{14}N_4O_2$, M = 330.34, monoclinic, $P2_1/c$, a = 5.7573(7) Å, b = 10.3774(12) Å, c = 25.578(3) Å, β = 93.948(5), V = 1524.6(3) $Å^3$, Z = 4, D_c = 1.439 g cm^{-3}, F_{000} = 688, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.48°, μ = 0.097 mm^{-1}, 17008 reflections collected, 3128 unique (R_{int} = 0.0479), final GooF = 1.266, R_1 = 0.0372, wR_2 = 0.0838 (2433 obs. data: $I > 2\sigma(I)$); R_1 = 0.0547, wR_2 = 0.0905 (all data). Full details are given in *Appendix III*.

Method B: *From BtMs* **176** *and acid*
This was prepared following the procedure described for **179** (Method B: From BtMS **176** and acid), from a solution of acid **122** (3.30 g, 14.40 mmol), BtMs **176** (2.84 g, 14.40 mmol) in tetrahydrofuran (60 mL) and triethylamine (2.3 mL, 20.15 mmol) to give the crude *acylbenzotriazole* as a bright orange solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) to (80:20) afforded the *acylbenzotriazole* **189** (0.77 g, 16%) as a white solid. Spectral properties were identical to those obtained above.*

* Trace amount of acid **122** starting material identified in purified mixture.

Synthesis of β-diketones/1,3-diketones from acylbenzotriazoles



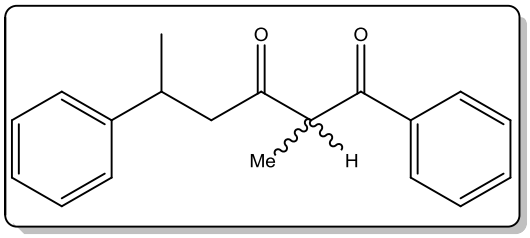
General numbering scheme for β-diketones

Initial workup of the crude β-diketones involved dilution with aqueous hydrochloric acid and this was later replaced by aqueous saturated ammonium chloride in the workup. The reason for this change was the possible loss of pyridine product after protonation by aqueous hydrochloric acid. The workup employed in each experiment is detailed in the experimental procedure.

Three conditions were used to prepare the β-diketones; Method A: hard enolisation using LiHMDS, Method B: soft enolisation using $MgBr_2 \cdot OEt_2$ and *N*,*N*-diisopropylethylamine and Method C: hard enolisation using LDA.

2-Methyl-1,5-diphenylhexane-1,3-dione 190a and 190b[167]

Method A: Hard enolisation using LiHMDS[199]



Lithium bis(trimethylsilyl)amide [(LiHMDS), (1.0 M in THF, 7.9 mL, 7.90 mmol)] was diluted in freshly distilled tetrahydrofuran (20 mL) and cooled to –80 °C. A solution of propiophenone (1.0 mL, 7.50 mmol) in tetrahydrofuran (10 mL) was added dropwise over 4 min. The reaction mixture was stirred at –80 °C for 1 h, then a tetrahydrofuran solution (10 mL) of acylbenzotriazole **178** (1.89 g, 7.50 mmol) was added in one portion; an orange/yellow colour was observed upon addition. The reaction mixture was warmed slowly to room temperature overnight. The reaction mixture was diluted with

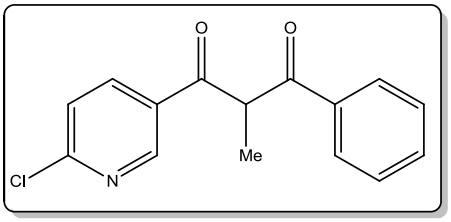
aqueous hydrochloric acid (2.0 M, 20 mL) and stirred for 10 min. The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate and concentrated to afford an orange/yellow oil. The resulting oil was redissolved in ether (100 mL), washed with aqueous hydrochloric acid (2.0 M, 3 × 20 mL), brine (20 mL) and concentrated *in vacuo* to provide the crude *diketone* as an orange/yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) gave the pure *1,3-diketone* **190a** and **190b** (1.36 g, 65%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.16 [1.5H, d, *J* 6.8, one of 2 × C(2')HC$\underline{H}_3$], 1.23 [1.6H, d, *J* 6.8, one of 2 × C(2')HC$\underline{H}_3$], 1.35 [3H, 2 × overlapping d, *J* 6.8, 6.8, C(5')HC$\underline{H}_3$], 2.60–2.91 [2H, m, C(4')$\underline{H}_2$], 3.31 [1H, 2 × overlapping q, *J* 6.8, 6.8, C(5')$\underline{H}$], 4.29 [0.5H, q, *J* 6.8, one of 2 × C(2')$\underline{H}$CH$_3$], 4.38 [0.5H, q, *J* 6.8, one of 2 × C(2')$\underline{H}$CH$_3$], 7.10–7.32 [5.5H, m, 5 × aromatic $\underline{H}$]*, 7.43 [2H, t, *J* 8.0, 2 × aromatic $\underline{H}$], 7.57 [1H, t, *J* 7.6, aromatic $\underline{H}$], 7.84 [2H, d with further splitting, *J* 8.0, 2 × aromatic $\underline{H}$]; HRMS (ES+): Exact mass calculated for $C_{19}H_{21}O_2$ $[M+H]^+$, 281.1542. Found 281.1533. m/z (ES+) 281.4 $[(M+H)^+$, 10%].

* Integration is higher than expected.

Method B: Soft enolisation using $MgBr_2{\cdot}OEt_2$ and N,N-*diisopropylethylamine*[200]
Propiophenone (0.6 mL, 4.55 mmol) was added to a suspension of acylbenzotriazole **178** (1.00 g, 3.77 mmol) and $MgBr_2{\cdot}OEt_2$ (2.44 g, 9.45 mmol) in dichloromethane (40 mL). This was followed by dropwise addition of diisopropylethylamine (2.0 mL, 11.36 mmol) and the suspension changed from colourless to yellow on addition of the diisopropylethylamine. The reaction mixture was stirred at room temperature for 4 h and subsequently quenched by addition of aqueous hydrochloric acid (3.2 M, 25 mL) and the mixture was stirred for 5 min. The aqueous layer was extracted with dichloromethane (3 × 50 mL) and the combined organic extracts were dried, filtered and concentrated under reduced pressure to give the crude *diketone* as a yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) gave the pure *1,3-diketone* **190a** and **190b** (1.05 g, 99%) as a colourless oil; ν_{max}/cm^{-1} (film) 2965, 1718, 1676, 1597, 1450, 1222, 701; The ^{1}H NMR spectral characteristics are consistent with those described above; δ_C (75.5 MHz, $CDCl_3$) isolated as an inseparable mixture of diastereomers 13.2 and 13.3 [CH_3, C(5')H$\underline{C}H_3$], 21.7 and 21.8 [CH_3, C(2')H$\underline{C}H_3$], 34.9 and 35.2 [CH, $\underline{C}$(5')H], 48.6 and 49.2 [CH_2, $\underline{C}$(4')H_2], 56.5 and 57.0 [CH, $\underline{C}$(2')HCH$_3$], 126.29 and 126.32 [CH, aromatic $\underline{C}$H], 126.7 and 126.8 [CH, 2 × aromatic $\underline{C}$H], 128.46 and 128.49 [CH, 2 × aromatic $\underline{C}$H], 128.6 and 128.8 [CH, 4 × aromatic $\underline{C}$H], 133.50 and 133.54 [CH, aromatic $\underline{C}$H], 135.9 and 136.0 [C, aromatic $\underline{C}$], 145.8 and 145.9 [C, aromatic $\underline{C}$], 197.0 and 197.3 [C, $\underline{C}$(1')=O or $\underline{C}$(3')=O], 205.7 and 206.0 [C, $\underline{C}$(1')=O or $\underline{C}$(3')=O].

3-(6-Chloropyridin-3-yl)-2-methyl-1-phenylpropane-1,3-dione 191

Method C: Hard enolisation using LDA[167]



n-Butyllithium (2.3 M in hexanes, 1.8 mL, 4.07 mmol) was added dropwise to freshly distilled diisopropylamine (0.5 mL, 3.87 mmol) in freshly distilled tetrahydrofuran (20 mL) at −80 °C under an atmosphere of nitrogen. The reaction mixture was stirred at −80 °C for 10 min. A solution of propiophenone (0.5 mL, 3.87 mmol) in

tetrahydrofuran (10 mL) was added dropwise over 4 min. The reaction mixture was stirred at –80 °C for 1 h, then a tetrahydrofuran solution (20 mL) of acylbenzotriazole **182** (1.00 g, 3.87 mmol) was added in one portion. A bright yellow solution was observed upon addition and the reaction mixture was warmed to room temperature overnight. The reaction mixture was diluted with aqueous hydrochloric acid (3.2 M, 20 mL) and stirred for 10 min; then the phases were separated. The aqueous phase was extracted with ether (2 × 50 mL) and the combined organic phases were washed with brine (30 mL), dried using magnesium sulfate and concentrated to give an orange oil. The resulting oil was redissolved in ether (80 mL) and washed with aqueous hydrochloric acid (3.2 M, 3 × 20 mL), brine (20 mL), dried and concentrated under reduced pressure to generate the crude *diketone* as a viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) gave the pure *1,3-diketone* **191** (0.67 g, 64%) as a pale yellow oil which later solidified to provide a pale yellow solid; m.p. 72–74 °C; ν_{max}/cm^{-1} (film) 2935, 1702, 1676, 1579, 1450, 1361, 1299, 1231, 1204, 1108, 970; δ_H (400 MHz, $CDCl_3$) 1.62 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$]*, 5.18 [1H, q, *J* 7.2, C(2')$\underline{H}$CH$_3$], 7.42 [1H, d, *J* 8.4, C(5")$\underline{H}$], 7.50 [2H, dd, *J* 8.0, 8.0, 2 × aromatic $\underline{H}$], 7.62 [1H, finely split t, *J* 7.6, aromatic $\underline{H}$], 7.96 [2H, dd, *J* 8.0, 0.8, 2 × aromatic $\underline{H}$], 8.17 [1H, dd, *J* 8.4, 2.4, C(4")$\underline{H}$], 8.87 [1H, d, *J* 2.4, C(2')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH$_3$, C(2')H$\underline{C}$H$_3$], 51.6 [CH, $\underline{C}$(2')HCH$_3$], 124.8 [CH, $\underline{C}$(5")H], 128.6 [CH, 2 × aromatic $\underline{C}$H], 129.1 [CH, 2 × aromatic $\underline{C}$H], 130.2 [C, $\underline{C}$(3")], 134.0 [CH, aromatic $\underline{C}$H], 135.1 [C, aromatic $\underline{C}$], 138.5 [CH, $\underline{C}$(4")H], 149.9 [CH, $\underline{C}$(2")H], 155.9 [C, $\underline{C}$(6")Cl], 194.6 and 196.9 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{15}H_{13}{}^{35}ClNO_2$ $[M+H]^+$, 274.0635. Found 274.0639. m/z (ES+) 276.3 {[($C_{15}H_{13}{}^{37}ClNO_2)^+$], 34%}, 274.3 {[($C_{15}H_{13}{}^{35}ClNO_2)^+$], 100%}.

* Integration is higher than expected due to presence of water.

Method A: Hard enolisation using LiHMDS
This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 3.0 mL, 3.0 mmol) diluted in freshly distilled tetrahydrofuran (10 mL), a solution of propiophenone (0.4 mL, 2.68 mmol) in tetrahydrofuran (10 mL), a solution (10 mL) of acylbenzotriazole **182** (0.70 g, 2.68 mmol) in tetrahydrofuran (10 mL) and saturated ammonium chloride (20 mL) in workup to provide the crude *1,3-diketone* as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (30:70) to (40:60) gave the *1,3-diketone* **191** (0.28 g, 38%) as a pale yellow oil. Spectral characteristics were consistent with those reported above.*

* The sample contains ~13 mol% propiophenone starting material.

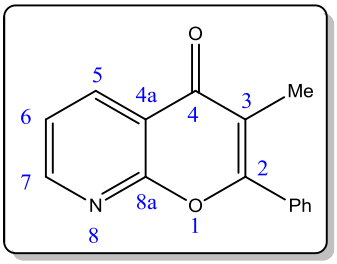
3-(2-Chloropyridin-3-yl)-2-methyl-1-phenylpropane-1,3-dione 192

Method C: Attempted formation of **192** via *hard enolisation using LDA*
This was prepared following the procedure described for **191** (Method C: Hard enolisation using LDA), from *n*-butyllithium (2.0 M in hexanes, 4.5 mL, 8.96 mmol) and freshly distilled diisopropylamine (1.2 mL, 8.51 mmol) diluted in tetrahydrofuran (20 mL), a solution of propiophenone (1.1 mL, 8.51 mmol) in tetrahydrofuran (10 mL), a solution of acylbenzotriazole **183** (2.20 g, 8.51 mmol) in tetrahydrofuran (10 mL) and saturated ammonium chloride (20 mL) in workup to generate the crude product as a viscous yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) to (40:60) generated an unexpected side product **201** as the major component as well

as trace amount of *1,3-diketone* **192**. The details for the major component **201** are described below.

Major product isolated from method C: Hard enolisation using LDA

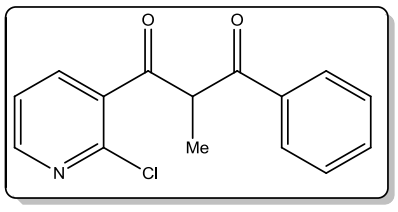
3-Methyl-2-phenyl-4*H*-pyrano[2,3-b]pyridin-4-one 201



White solid (0.47 g); m.p. 113–115 °C; ν_{max}/cm^{-1} (KBr) 2914, 1642, 1601, 1474, 1424, 1389; δ_H (400 MHz, $CDCl_3$)* 2.20 [3H, s, C(3)C<u>H</u>$_3$], 7.45 [1H, dd, *J* 8.0, 4.8, C(6)<u>H</u>], 7.52–7.54 [3H, m, 3 × aromatic <u>H</u>], 7.70–7.74 [2H, m, 2 × aromatic <u>H</u>], 8.64 [1H, dd, *J* 7.6, 2.0, C(5)<u>H</u>], 8.70 [1H, overlapping dd, *J* 4.8, 2.0, C(7)<u>H</u>]; δ_C (125.8 MHz, $CDCl_3$) 11.9 [CH_3, C(3)<u>C</u>H_3], 117.2 [C, <u>C</u>(3)CH_3 or <u>C</u>(4)a], 118.1 [C, <u>C</u>(3)CH_3 or <u>C</u>(4a)], 121.8 [CH, <u>C</u>(6)H], 128.5 [CH, 2 × aromatic <u>C</u>H], 129.2 [CH, 2 × aromatic <u>C</u>H], 130.6 [CH, aromatic <u>C</u>H], 132.8 [C, aromatic <u>C</u>], 136.6 [CH, <u>C</u>(5)H], 153.2 [CH, <u>C</u>(7)H], 160.5 [C, <u>C</u>(8)a or <u>C</u>(2)C_6H_5], 161.6 [C, <u>C</u>(8a) or <u>C</u>(2)C_6H_5], 179.4 [C, <u>C</u>(4)=O]; HRMS (ES+): Exact mass calculated for $C_{15}H_{12}NO_2$ $[(M+H)^+]$, 238.0868. Found 238.0857. m/z (ES+) 238.3 $[(M+H)^+$, 100%]. ^{1}H NMR and ^{13}C NMR structural assignment was aided by COSY and HSQC 2D NMR experiments as well as comparison with related compounds prepared by Fu.[204]

Single crystals of 3-methyl-2-phenyl-4*H*-pyrano[2,3-b]pyridin-4-one **201** were grown from deuterated chloroform. Crystal data: $C_{15}H_{11}NO_2$, M = 237.25, monoclinic, $P2_1/n$, a = 3.822(2) Å, b = 20.502(13) Å, c = 13.574(9) Å, β = 95.084(13)°, V = 1059.5(12) Å^3, Z = 4, D_c = 1.487g cm^{-3}, F_{000} = 496, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 25.07°, μ = 0.100 mm^{-1}, 4719 reflections collected, 1729 unique (R_{int} = 0.1453), final GooF = 0.954, R_1 = 0.0817, wR_2 = 0.1926 (885 obs. data: $I > 2\sigma(I)$); R_1 = 0.1598, wR_2 = 0.2400 (all data). Full details are given in *Appendix III*.

Method A: Hard enolisation using LiHMDS

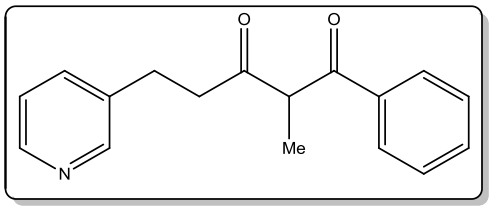


This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 4.3 mL, 4.30 mmol) diluted in freshly distilled tetrahydrofuran (10 mL), a solution of propiophenone (0.5 mL, 3.87 mmol) in tetrahydrofuran (10 mL), a tetrahydofuran solution (10 mL) of acylbenzotriazole **183** (1.00 g, 3.87 mmol) and saturated ammonium chloride (20 mL) in workup to provide the crude mixture of *diketone* **192** and *side product* **201** as a viscous orange/yellow oil in ratio of **192** : **201** 76 : 24. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) furnished the *1,3-diketone* **192** (0.15 g, 14%)* and this was isolated as the less polar fraction; ν_{max}/cm^{-1} (film) 2921, 1751, 1641, 1578, 1561, 1405, 1260,

1221, 1128, 1050, 758; δ_H (400 MHz, $CDCl_3$) 1.81 [3H, d, *J* 6.8, C(2')HC$\underline{H}_3$], 6.00 [1H, q, *J* 7.2, C(2')$\underline{H}CH_3$], 7.26–7.37 [3H, m, 3 × aromatic $\underline{H}$], 7.41 [1H, dd, *J* 8.0, 4.8, C(5")$\underline{H}$], 7.46 [2H, dd, *J* 8.8, 1.6, 2 × aromatic $\underline{H}$], 8.39 [1H, dd, *J* 8.0, 2.0, C(4")$\underline{H}$], 8.60 [1H, dd, *J* 4.8, 2.0, C(6")$\underline{H}$]. A more polar fraction was isolated as a white solid (0.44 g, 41%) and the spectral properties were in agreement to those obtained for side product **201** from method C.**

* Contains ~15 mol% side product **201** and possibly some of the enol tautomer.
** Sample contains trace of diketone **192** as well as ~28 mol% 1*H*-benzotriazole **175**.

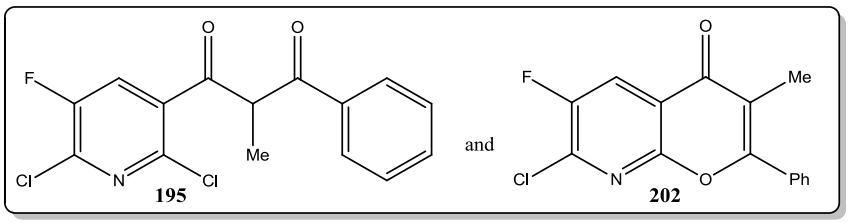
2-Methyl-1-phenyl-5-(pyridin-3-yl)pentane-1,3-dione 194



This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 1.9 mL, 1.90 mmol) diluted in freshly distilled tetrahydrofuran (10 mL), propiophenone (0.2 mL, 1.72 mmol) dissolved in tetrahydrofuran (10 mL), a tetrahydrofuran solution (10 mL) of acylbenzotriazole **180** (0.43 g, 1.72 mmol) and saturated ammonium chloride (20 mL) in the workup to provide the crude *diketone* as a crystalline white solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *1,3-diketone* **194** (0.05 g, 10%) as a colourless oil*; ν_{max}/cm^{-1} (film) 2918, 1719, 1676, 1654, 1597, 1575, 1449, 1422; δ_H (400 MHz, $CDCl_3$) 1.41 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 2.68–2.89 [4H, m, C(4')$\underline{H}_2$ and C(5')$\underline{H}_2$], 4.46 [1H, q, *J* 6.8, C(2')$\underline{H}CH_3$], 7.13 [1H, dd, *J* 7.2, 4.8, C(5")$\underline{H}$], 7.41–7.47 [3H, m, 3 × aromatic $\underline{H}$], 7.58 [1H, t with further splitting, *J* 7.6, C(4")$\underline{H}$], 7.90 [2H, d, *J* 8.0, 2 × aromatic $\underline{H}$], 8.36–8.40 [2H, m, C(2")$\underline{H}$ and C(6")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 13.6 [CH_3, C(2')H$\underline{C}H_3$], 26.6 [CH_2, $\underline{C}$(5')H_2], 41.6 [CH_2, $\underline{C}$(4')H_2], 56.2 [CH, $\underline{C}$(2')HCH_3], 123.3 [CH, $\underline{C}$(5")H], 128.6 [CH, 2 × aromatic $\underline{C}$H], 128.9 [CH, 2 × aromatic $\underline{C}$H], 133.8 [CH, aromatic $\underline{C}$H], 135.8 [C, aromatic $\underline{C}$ or $\underline{C}$(3")], 135.9 [CH, $\underline{C}$(4")H], 136.0 [C, aromatic $\underline{C}$ or $\underline{C}$(3")], 147.7 [CH, $\underline{C}$(2")H or $\underline{C}$(6")H], 149.9 [CH, $\underline{C}$(2")H or $\underline{C}$(6")H], 197.3 and 205.5 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{17}H_{18}NO_2$ $[M+H]^+$, 268.1338. Found 268.1339. m/z (ES+) 268.3 $[(M+H)^+$, 100%].

* Sample contains a significant amount of ethyl acetate.

3-(2,6-Dichloro-5-fluoropyridin-3-yl)-2-methyl-1-phenylpropane-1,3-dione 195 and 7-Chloro-6-fluoro-3-methyl-2-phenyl-4*H*-pyrano[2,3-b]pyridin-4-one 202



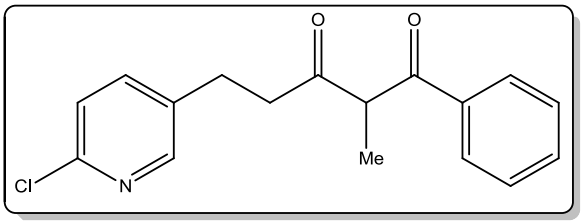
This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 7.6 mL, 7.60 mmol) diluted in freshly distilled tetrahydrofuran (10 mL), a solution of propiophenone (0.9 mL, 6.88 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (20 mL) of acylbenzotriazole **184** (2.14 g, 6.88 mmol) and saturated ammonium chloride (20 mL) in workup to furnish the crude *diketone* as a viscous orange/yellow oil*. Repeated purification by flash chromatography on

silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) gave the *1,3-diketone* **195** (0.69 g, 31%) as a red/orange oil**; ν_{max}/cm^{-1} (film) 3067, 1718, 1676, 1596, 1554, 1450, 1403, 1125, 970, 719, 704 ; δ_H (400 MHz, $CDCl_3$) 1.58 [3H, d, *J* 6.8, C(2')HC$\underline{H}_3$], 5.44 [1H, q, *J* 7.2, C(2')$\underline{H}CH_3$], 7.46–7.53 [3H, m, 5 × aromatic $\underline{H}$], 7.73 [1H, d, J_{HF} 7.2, C(4")$\underline{H}$], 7.93 [2H, dd, *J* 8.0, 1.2, 2 × aromatic $\underline{H}$]; HRMS (ES+): Exact mass calculated for $C_{15}H_{11}{}^{37}Cl^{35}ClNO_2$ $[M+H]^+$, 328.0121. Found 328.0106 and exact mass calculated for $C_{15}H_{11}{}^{35}Cl_2FNO_2$ $[M+H]^+$, 326.0151. Found 326.0136. m/z (ES+) 326.15 {$[(C_{15}H_{11}{}^{35}Cl_2FNO_2)^+]$, tentatively located}, 279.4 (100%).

* Crude product contains ~13 mol% side product **202** which is tentatively assigned with peaks at δ_H 2.20 ppm [0.54H, s], one of δ_H 8.05 or 8.18 ppm [0.18H, d, J_{HF} 7.2].
** Extra peaks at δ_H 1.84 ppm [1.62H, s], 7.58 ppm [0.62H, d, J_{HF} 7.2], 7.59–7.64 ppm [2H, m] and 16.34 ppm [0.43H, s] were tentatively ascribed to the enol tautomer (~32 mol%) by comparative integration of signals.

5-(6-Chloropyridin-3-yl)-2-methyl-1-phenylpentane-1,3-dione 196

Method A: Hard enolisation using LiHMDS

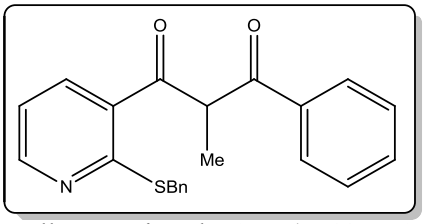


This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 2.5 mL, 2.50 mmol) diluted in freshly distilled tetrahydrofuran (10 mL) , a solution of propiophenone (0.3 mL, 2.32 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (20 mL) of acylbenzotriazole **185** (0.66 g, 2.32 mmol) and saturated ammonium chloride (20 mL) in the workup to afford the crude diketone as a viscous yellow oil. Purification by column chromatography with ethyl acetate/hexane (30:70) gave the pure *1,3-diketone* **196** (0.40 g, 67%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 1.40 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 2.61–2.88 [4H, m, C(4')$\underline{H}_2$ and C(5')$\underline{H}_2$], 4.46 [1H, q, *J* 7.2, C(2')$\underline{H}CH_3$], 7.11 [1H, d, *J* 8.4, C(5")$\underline{H}$], 7.37 [1H, dd, *J* 8.4, 2.8, C(4")$\underline{H}$], 7.44 [2H, dd, *J* 8.0, 8.0, 2 × aromatic $\underline{H}$], 7.58 [1H, finely split triplet, *J* 7.2, aromatic $\underline{H}$], 7.86 [2H, d, *J* 7.2, 2 × aromatic $\underline{H}$], 8.12 [1H, d, *J* 2.4, C(2")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 13.5 [CH_3, C(2')H$\underline{C}H_3$], 25.7 [CH_2, $\underline{C}$(5')H_2], 41.2 [CH_2, $\underline{C}$(4')H_2], 56.2 [CH, $\underline{C}$(2')HCH_3], 123.8 [CH, $\underline{C}$(5")H], 128.5 [CH, 2 × aromatic $\underline{C}$H], 128.9 [CH, 2 × aromatic $\underline{C}$H], 133.8 [CH, aromatic $\underline{C}$H], 134.9 [C, aromatic $\underline{C}$ or $\underline{C}$(3")], 135.6 [C, aromatic $\underline{C}$ or $\underline{C}$(3")], 138.8 [CH, $\underline{C}$(4")H], 149.2 [C, $\underline{C}$(6")Cl], 149.4 [CH, $\underline{C}$(2")H], 197.1 and 205.2 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O].

Method C: Hard enolisation using LDA
This was prepared following the procedure used for **191** (Method C: Hard enolisation using LDA), from *n*-butyllithium (1.98 M in hexanes, 1.8 mL, 3.66 mmol), freshly distilled diisopropylamine in freshly distilled tetrahydrofuran (40 mL), a solution of propiophenone (0.5 mL, 3.48 mmol) in tetrahydrofuran (10 mL) and a tetrahydrofuran solution (20 mL) of acylbenzotriazole **185** (1.00 g, 3.48 mmol) and aqueous hydrochloric acid (3.2 M, 20 mL) in workup to afford the crude *diketone* as a viscous light yellow oil. Purification by column chromatography with ethyl acetate/hexane (5:95) to (10:90) to (20:80) gave the *1,3-diketone* **196** (0.24 g, 23%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 1736, 1460, 1451, 1382, 1107, 965; ^{1}H NMR properties were consistent with those obtained above; HRMS (ES+): Exact mass calculated for $C_{17}H_{17}{}^{37}ClNO_2$ $[M+H]^+$, 304.0918. Found 304.0917 and exact mass calculated

for $C_{17}H_{17}{}^{35}ClNO_2$ $[M+H]^+$, 302.0948. Found 302.0941 m/z (ES+) 301.3 $\{[(C_{17}H_{17}{}^{35}ClNO_2)^+]$, 15%$\}$.

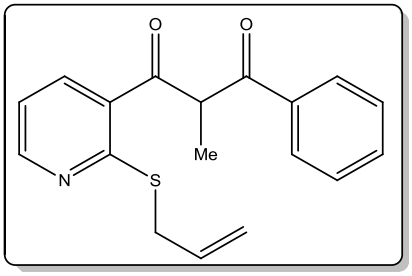
3-[2-(Benzylthio)pyridin-3-yl]-2-methyl-1-phenylpropane-1,3-dione 197



This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 1.8 mL, 1.80 mmol) diluted in freshly distilled tetrahydrofuran (20 mL), a solution of propiophenone (0.2 mL, 1.84 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (10 mL) of acylbenzotriazole **186** (0.64 g, 1.84 mmol) and saturated ammonium chloride (20 mL) in the workup to furnish the crude *diketone* as a viscous yellow/orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) gave the pure *1,3-diketone* **197** (0.38 g, 57%) as a pale yellow oil; ν_{max}/cm^{-1} (film) 2936, 1690, 1670, 1597, 1578, 1544, 1451, 1392, 1288, 1200, 968, 702; δ_H (400 MHz, $CDCl_3$) 1.57 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 4.39 [1H, A of AB, *J* 13.2, one of SC$\underline{H}_2C_6H_5$], 4.46 [1H, B of AB, *J* 13.2, one of SC$\underline{H}_2C_6H_5$], 5.16 [1H, q, *J* 7.2, C(2')$\underline{H}CH_3$], 7.01 [1H, dd, *J* 8.0, 4.8, C(5")$\underline{H}$], 7.18–7.29 [3H, m, 3 × aromatic $\underline{H}$], 7.36–7.44 [4H, m, 4 × aromatic $\underline{H}$]*, 7.53–7.57 [1H, ddd, *J* 7.6, 5.6, 1.2, aromatic $\underline{H}$], 7.88–7.90 [2H, dd, *J* 8.0, 1.2, 2 × aromatic $\underline{H}$], 7.93 [1H, dd, *J* 7.6, 2.0, C(4")$\underline{H}$], 8.53 [1H, dd, *J* 4.4, 2.0, C(6")$\underline{H}$]; δ_C (125.8 MHz, $CDCl_3$) 14.3 [CH_3, C(2')H$\underline{C}H_3$], 35.1 [CH_2, S$\underline{C}H_2C_6H_5$], 52.8 [CH, $\underline{C}$(2')HCH$_3$], 118.3 [CH, $\underline{C}$(5")H], 126.9 [CH, aromatic $\underline{C}$H], 128.3 [CH, 2 × aromatic $\underline{C}$H], 128.6 [CH, 2 × aromatic $\underline{C}$H], 128.8 [C, $\underline{C}$(3")], 128.9 [CH, 2 × aromatic $\underline{C}$H], 129.3 [CH, 2 × aromatic $\underline{C}$H], 133.6 [CH, aromatic $\underline{C}$H], 135.4 [C, aromatic $\underline{C}$], 137.4 [CH, $\underline{C}$(4")H], 137.7 [C, aromatic $\underline{C}$], 151.6 [CH, $\underline{C}$(6")H], 161.6 [C, $\underline{C}$(2")SCH$_2$C$_6$H$_5$], 196.9 and 197.1 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{22}H_{20}NO_2S$ $[M+H]^+$, 362.1215. Found 362.1212. m/z (ES+) 362.2 $[(M+H)^+$, 32%].

***** Integration is higher than expected.

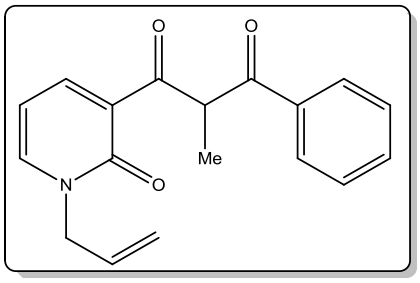
3-[2-(Allylthio)pyridin-3-yl]-2-methyl-1-phenylpropane-1,3-dione 198



This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 3.4 mL, 3.40 mmol) diluted in freshly distilled tetrahydrofuran (20 mL), a solution of propiophenone (0.4 mL, 3.07 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (10 mL) of acylbenzotriazole **187** (0.91 g, 3.07 mmol) and saturated ammonium chloride (20 mL) in the workup to provide the crude *diketone* as a viscous yellow/orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (20:80) to (30:70) to (60:40) afforded the pure *1,3-diketone* **198** (0.654 g, 68%) as a pale yellow oil which smelled strongly of garlic; ν_{max}/cm^{-1} (film) 2982, 1691, 1670, 1597, 1578, 1545, 1450, 1393, 1199, 969; δ_H (400 MHz, $CDCl_3$) 1.56 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 3.79–.84 [2H, m, SC$\underline{H}_2$CHCH$_2$], 5.05 [1H, br d with further unresolved splitting, *J* 10.0, one of SCH$_2$CHC$\underline{H}_2$], 5.19–5.27 [2H, m, overlapping of one of SCH$_2$CHC$\underline{H}_2$ and C(2')$\underline{H}$CH$_3$], 5.86–5.98 [1H, m, SCH$_2$C$\underline{H}$CH$_2$], 6.99 [1H, dd, *J* 8.0, 4.8 C(5")$\underline{H}$], 7.42

[2H, dd, *J* 8.0, 8.0, 2 × aromatic H], 7.53 [1H, ddd, *J* 9.2, 5.2, 1.6, aromatic H], 7.88–7.95 [3H, m, overlapping d and dd, 2 × aromatic H and C(4")H], 8.48 [1H, dd, *J* 4.8, 0.8, C(6")H]; δ_C (125.8 MHz, $CDCl_3$) 14.2 [CH_3, C(2')H$\underline{C}H_3$], 33.3 [CH_2, S$\underline{C}H_2CHCH_2$], 52.6 [CH, $\underline{C}$(2')HCH_3], 117.7 [CH_2, $SCH_2CH\underline{C}H_2$], 118.2 [CH, $\underline{C}$(5")H], 128.6 [CH, 2 × aromatic CH], 128.9 [CH, 2 × aromatic CH], 129.0 [C, $\underline{C}$(3")], 133.6 and 133.7 [2 × CH, aromatic CH and $SCH_2\underline{C}HCH_2$], 135.4 [C, aromatic C], 137.3 [CH, $\underline{C}$(4")H], 151.5 [CH, $\underline{C}$(6")H], 161.3 [C, $\underline{C}$(2")SCH_2CHCH_2], 196.9 and 197.1 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{18}H_{18}NO_2S$ $[M+H]^+$, 312.1058. Found 312.1058. m/z (ES+) 312.2 $[(M+H)^+$, 100%].

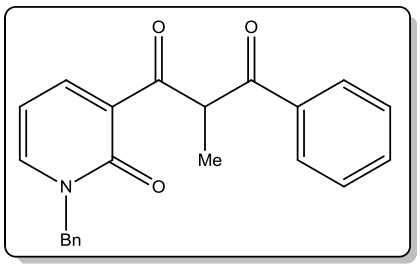
3-(1-Allyl-2-oxo-1,2-dihydropyridin-3-yl)-2-methyl-1-phenylpropane-1,3-dione 199



This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 3.3 mL, 3.30 mmol) diluted in freshly distilled tetrahydrofuran (20 mL), a solution of propiophenone (0.4 mL, 3.28 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (10 mL) of acylbenzotriazole **188** (0.92 g, 3.28 mmol) and saturated ammonium chloride (20 mL) in the workup to afford the crude *diketone* as a viscous yellow/orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) to (20:80) furnished the pure N-*allyl 1,3-diketone* **199** (0.31 g, 32%)* as a pale yellow oil; ν_{max}/cm^{-1} (film) 3084, 2985, 1684, 1652, 1588, 1542, 1458, 1450, 1309, 1285, 1234, 1203, 976, 768, 702; δ_H (400 MHz, $CDCl_3$) 1.44 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 4.43 [1H, ddt, *J* 15.2, 6.0, 1.2, one of NC$\underline{H}_2CHCH_2$], 4.59 [1H, ddt, *J* 15.2, 6.0, 1.6, one of NC$\underline{H}_2CHCH_2$], 5.14 [1H, dd, *J* 16.8, 0.8, one of $NCH_2CHC\underline{H}_2$], 5.24 [1H, dd, *J* 10.0, 0.8, one of $NCH_2CHC\underline{H}_2$], 5.74–5.91 [2H, m, overlapping 2 × CH, C(2')$\underline{H}CH_3$ and $NCH_2C\underline{H}CH_2$], 6.32 [1H, dd, *J* 7.2, 7.2, C(5")H], 7.44 [2H, dd, *J* 8.0, 8.0, 2 × aromatic H], 7.49–7.54 [2H, m, aromatic H and C(6")H], 8.02 [2H, d, *J* 7.2, 2 × aromatic H], 8.25 [1H, dd, *J* 7.2, 2.0, C(4")H]; δ_C (125.8 MHz, $CDCl_3$) 13.3 [CH_3, C(2')H$\underline{C}H_3$], 51.3 [CH_2, N$\underline{C}H_2CHCH_2$], 53.6 [CH, $\underline{C}$(2')HCH_3], 106.0 [CH, $\underline{C}$(5")H], 119.1 [CH_2, $NCH_2CH\underline{C}H_2$], 126.0 [C, $\underline{C}$(3")], 128.5 [CH, 2 × aromatic CH], 128.7 [CH, 2 × aromatic CH], 131.8 [CH, aromatic CH or $NCH_2\underline{C}HCH_2$], 132.7 [CH, aromatic CH or $NCH_2\underline{C}HCH_2$], 136.2 [C, aromatic C], 142.5 [CH, $\underline{C}$(4")H or $\underline{C}$(6")H], 144.3 [CH, $\underline{C}$(4")H or $\underline{C}$(6")H], 160.6 [C, $\underline{C}$(2")=O], 196.6 and 199.3 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{18}H_{18}NO_3$ $[M+H]^+$, 296.1287. Found 296.1282. m/z (ES+) 295.3 $[(M)^+$, tentatively located].

* Sample contains ~12 mol% of 1*H*-benzotriazole **175**.

3-(1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)-2-methyl-1-phenylpropane-1,3-dione 200



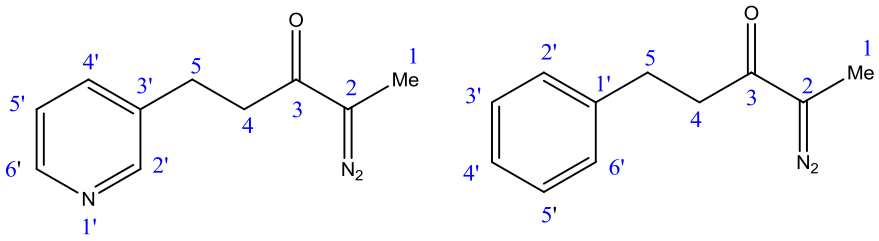
This was prepared following the procedure described for **190** (Method A: Hard enolisation using LiHMDS), from LiHMDS (1.0 M in THF, 1.9 mL, 1.90 mmol) diluted in freshly distilled tetrahydrofuran (20 mL), a solution of propiophenone (0.3 mL, 1.85 mmol) in tetrahydrofuran (10 mL), a tetrahydrofuran solution (30 mL) of

acylbenzotriazole **189** (0.61 g, 1.85 mmol) and saturated ammonium chloride (20 mL) in the workup to give the crude *diketone* as a viscous yellow/orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) to (30:70) furnished the *1,3-diketone* **200** (0.43 g, 67%)* as a colourless oil; ν_{max}/cm^{-1} (film) 2982, 1686, 1596, 1583, 1542, 1450, 1221, 746; δ_H (400 MHz, $CDCl_3$) 1.48 [3H, d, *J* 7.2, C(2')HC$\underline{H}_3$], 5.03 [1H, A of AB, *J* 14.8, one of NC$\underline{H}_2C_6H_5$], 5.13 [1H, B of AB, *J* 14.8, one of NC$\underline{H}_2C_6H_5$], 5.82 [1H, q, *J* 7.2, C(2')$\underline{H}CH_3$], 6.31 [1H, dd, *J* 7.2, 7.2, C(5")$\underline{H}$], 7.13 [2H, br overlapping dd, *J* 7.2, 3.2, 2 × aromatic $\underline{H}$], 7.23–7.29 [3H, m, 3 × aromatic $\underline{H}$], 7.37 [2H, t, *J* 7.2, 2 × aromatic $\underline{H}$], 7.45–7.52 [2H, m, overlapping 2 × CH, aromatic $\underline{H}$ and C(6")$\underline{H}$], 8.03 [2H, d, *J* 7.2, 2 × aromatic $\underline{H}$], 8.27 [1H, dd, *J* 7.6, 2.4, C(4")$\underline{H}$]; δ_C (125.8 MHz, $CDCl_3$)** 13.5 [CH_3, C(2')H$\underline{C}H_3$], 52.4 [CH_2, N$\underline{C}H_2C_6H_5$], 53.8 [CH, $\underline{C}$(2')HCH$_3$], 106.4 [CH, $\underline{C}$(5")H], 126.2 [C, $\underline{C}$(3")], 128.0 [CH, 2 × aromatic $\underline{C}$H], 128.3 [CH, aromatic $\underline{C}$H], 128.6 [CH, 2 × aromatic $\underline{C}$H], 128.8 [CH, 2 × aromatic $\underline{C}$H], 129.0 [CH, 2 × aromatic $\underline{C}$H], 132.9 [CH, aromatic $\underline{C}$H], 135.3 [C, aromatic $\underline{C}$], 136.2 [C, aromatic $\underline{C}$], 142.7 [CH, $\underline{C}$(4")H or $\underline{C}$(6")H], 144.4 [CH, $\underline{C}$(4")H or $\underline{C}$(6")H], 161.1 [C, $\underline{C}$(2")=O], 196.7 and 199.7 [2 × C, $\underline{C}$(1')=O and $\underline{C}$(3')=O]; HRMS (ES+): Exact mass calculated for $C_{22}H_{20}NO_3$ $[M+H]^+$, 346.1443. Found 346.1445. m/z (ES+) 346.3 $[(M+H)^+$, 100%].

* The 1*H*-benzotriazole **175** side product (~61 mol%) was found to co-elute with 1,3-diketone **200** as confirmed by ^{1}H NMR analysis showing distinctive sextets ~δ_H 7.43 ppm [2H, m, C(5)$\underline{H}$ and C(6)$\underline{H}$] and ~δ_H 7.94 ppm [2H, m, C(4)$\underline{H}$ and C(7)$\underline{H}$].

** The product was isolated as a mixture of 1*H*-benzotriazole **175** and 1,3-diketone **200** with ^{13}C NMR run on this sample. The peaks corresponding to 1*H*-benzotriazole were identified by comparison with a purified sample of 1*H*-benzotriazole **175**. The relevant peaks for **175** were located at δ_C 115.1 ppm [CH, $\underline{C}$(4)H and $\underline{C}$(7)H], 126.1 ppm [$\underline{C}$(5)H and $\underline{C}$(6)H] and 139.0 ppm [C, $\underline{C}$(3)a and $\underline{C}$(7)a]. All remaining peaks in the ^{13}C NMR belong to 1,3-diketone **200**.

Synthesis of α-diazoketones

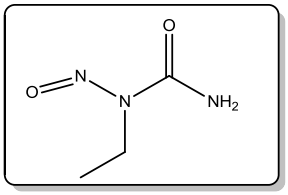


General numbering scheme for a-diazoketones

In ^{1}H NMR spectra of the α-diazoketones, the signal due to the methyl group, C(1)$\underline{H}_3$ (δ_H 1.91–1.94 ppm for unconjugated α-diazoketones, δ_H 2.07–2.10 ppm for conjugated α-diazoketones) was broadened relative to the remaining signals. Also, the presence of rotamers was observed in some cases as a broad singlet for the minor rotamer (~10%) which was in close proximity to the broadened signal for C(1)$\underline{H}_3$ at δ_H ~1.91–1.94 or 2.07–2.10 ppm. Integration of both rotameric signals for C(1)$\underline{H}_3$ corresponds to three hydrogens. For the unconjugated α-diazoketones, the signal corresponding to C(4)$\underline{H}_2$ was also broadened and an adjacent signal for the minor rotamer was identified at δ_H ~2.66–2.80 ppm (~10%) for compounds **134-139**.

Furthermore, ^{13}C NMR analysis demonstrated that signals for both $\underline{C}(1)H_3$ (δ_C ~8.0–8.4 ppm) and $\underline{C}(2)N_2$ (δ_C ~62.3 ppm) were in general broadened and therefore appeared weak, relative to the remaining signals. This is a spectral characteristic of all α-diazoketones that is due to restricted rotation of the bonds in close proximity to the diazo functional group.

N-Ethyl-*N*-nitrosourea 62[65]

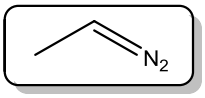


Aqueous ethylamine (70%, 241.2 mL) was placed with water (115 mL) in a 1 L round-bottomed flask. Concentrated hydrochloric acid (37%, *ca*. 310 mL) was added slowly until the solution was strongly acidic. Water (*ca*. 204 mL) was then added. This was carried out at 0 °C. Urea (>99.5%, 600 g) was added over 10 min and the solution was heated under gentle reflux for 2.5 h and then vigorously for 30 min. The solution was then cooled to room temperature and sodium nitrite (210 g) was added. Once the sodium nitrite had dissolved the solution was cooled to 0 °C and added slowly over 50 min to a mechanically stirred mixture of conc. Sulfuric acid (110 mL) and ice (1.20 kg) cooled at –20 °C using an ice-salt bath. *N*-Ethyl-*N*-nitrosourea formed as a foamy precipitate which was collected by suction filtration and washed with ice-cooled water (3 × 40 mL) to give **62** as a pale yellow powder (150 g), which was stored in the freezer at –20 °C in a sealed bottle. Due to the hazardous nature of this compound it was not considered advisable to conduct ^1H NMR or infrared analysis.

CAUTION!! N-*Ethyl*-N-*nitrosourea* **62** *is a carcinogen and therefore was handled with great care. Several pairs of gloves were worn when handling it and all procedures were carried out in a well-ventilated fumehood. All glassware was treated with potassium hydroxide (KOH) pellets to generate diazoethane* **20** *gas and left in the fumehood overnight. The next day the glassware was washed with acetic acid solution (33%) until acidified (checked with litmus paper).*

* The procedure described above for the preparation of *N*-ethyl-*N*-nitrosourea **62** is a modification of the procedure described for the preparation of *N*-methyl-*N*-nitrosourea.[293,294]

Diazoethane 20[65]



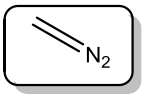
N-Ethyl-*N*-nitrosourea **62** (25.00 g, 214 mmol*) was added portionwise over 20 min to a mixture of ether (160.0 mL) and aqueous potassium hydroxide (50% w/w, 68.0 mL) while stirring at –20 °C. Once the addition was complete the reaction mixture was stirred for a further 30 min at –20 °C. The ether was then decanted and the solution was then dried over 3 portions of potassium hydroxide pellets cooled at –20 ºC to give an orange coloured ethereal solution of diazoethane **20** gas which was used immediately and was freshly prepared each time before use.

* It is important that approximately 7 equiv. of *N*-ethyl-*N*-nitrosourea **62** is used relative to the number of moles of acid chloride/carboxylic acid to be reacted. This excess is required as 7 equiv. of *N*-ethyl-*N*-nitrosourea **62** does not correspond to 7 equiv. of diazoethane **20** as the amount of diazoethane present is not known and would vary from reaction to reaction.

Caution! *Diazoethane* **20** *is toxic and explosive. All operations were carried out in a well-ventilated fumehood, with adequate shielding. The glassware used for the generation of* **20**

was free from cracks. Several pairs of gloves were worn during operation and all glassware which came into contact with diazoethane solution **20** *was washed with acetic acid solution (~33%) and left overnight in the fumehood to ensure all traces of diazoethane* **20** *were gone. The resultant washings were disposed by pouring down the sink and flushing with water.*

Diazomethane 15[295]



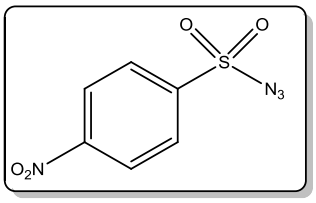
Diazald® [(*N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide), (1.20 g, 5.60 mmol)] dissolved in ether (10 mL) was added dropwise over ~30 min to a solution of potassium hydroxide (0.45 g, 8.06 mmol) in ethanol (95%, 1.8 mL) and water (0.45 mL) while stirring at ~70 °C (the oil bath was maintained at 70 °C using a contact thermometer). The rate of addition was regulated so the addition of the solution of Diazald® coincided with the distillation of one drop of diazomethane. Once addition was complete, ether (5 mL) was added and distillation was continued until most of the ether had distilled across, to give a solution of diazomethane in ether, which was freshly prepared each time before use.

Caution! *Diazomethane (b.p. –23 °C) is highly toxic, explosive, acid sensitive and carcinogenic. The preparation should be carried out in a well-ventilated fumehood with adequate shielding. Explosive decomposition of diazomethane can be initiated by sharp surfaces. Therefore, only glassware with clear joints should be used for distillation. Also, the distillation apparatus should not be exposed to strong sun or artificial light as diazomethane is photochemically labile.*

Note: a) Small quantities of diazomethane were used and the reaction mixture was stirred open in the fumehood on completion of the reaction for ~30 min to allow excess diazomethane to evaporate. All glassware which came in contact with diazomethane was washed with aqueous acetic acid (33%) to ensure complete removal of any residual diazomethane. In instances where the reaction mixture was evaporated under reduced pressure, the rotary evaporator was fitted with aqueous acetic acid in the solvent collection bulbs.

b) Commercial trimethylsilyldiazomethane **131** was used instead of diazomethane in some reactions. As trimethylsilyldiazomethane is light sensitive, all reactions were conducted in the dark with the reaction vessel also covered with tinfoil.

p-Nitrobenzenesulfonyl azide (*p*-NBSA) 166*



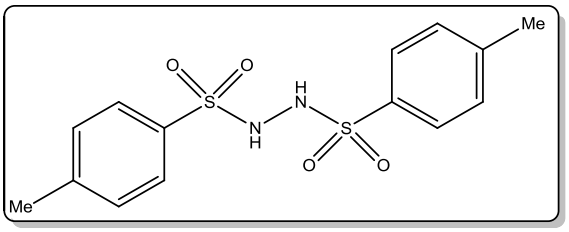
p-Nitrobenzenesulfonyl chloride [(*p*-NBSCl), (25.00 g, 113 mmol)] was dissolved in acetone (250 mL) and placed in a 2 L conical flask while stirring at room temperature. Sodium azide (8.80 g, 135 mmol) was weighed out in the fumehood, dissolved in water (120 mL), decanted slowly into the conical flask with the reaction stirred at room temperature for 24 h and the conical flask covered by a clock-glass. A pale yellow colour was observed at this point. After stirring for 24 h, the reaction mixture was poured onto water (1.5 L) with a pale yellow colour as well as a granular appearance observed. This was then stirred for 4 h at room temperature with a gradual precipitation of the product observed. The solid was collected by vacuum filtration and subsequently dried in a desiccator with potassium hydroxide as drying agent for ~5 days to give the crude *azide* **166** (23.98 g, 93%) as a pale yellow solid.

* The procedure described above for the preparation of *p*-nitrobenzenesulfonyl azide **166** is simply a modification of the procedure described for the preparation of *p*-acetamidobenzensulfonyl azide **203**.[296]

Caution! *Sodium azide is toxic and explosive. The weighing of this should be conducted in a well-ventilated fumehood.*

Note: The aqueous filtrate in the workup contains some excess azide and this must be quenched using the following procedure.[297] Approximately ~7 mL (20%, w/w) aqueous solution of sodium nitrite per gram of sodium azide used is added with stirring. An aqueous sulfuric acid solution (20%, v/v) is added until the reaction mixture is classed as acidic on turning blue litmus paper red. Once no more nitrogen is given off the acidified solution is tested with starch iodide which turns blue meaning the decomposition of the excess sodium azide is complete before disposal. The order of addition is essential, as addition of the acid before the nitrite will result in the evolution of hydrazoic acid (HN_3) which is a poisonous and highly explosive gas.

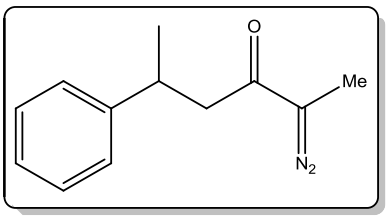
N,N'-Ditosylhydrazine 153[144]



A suspension of *p*-toluenesulfonyl hydrazide (9.32 g, 50.04 mmol) and *p*-toluenesulfonyl chloride (14.30 g, 75.0 mmol) in doubly distilled dichloromethane (50 mL) was stirred at room temperature for 10 min. Anhydrous pyridine (6.00 mL, 75.0 mmol) was added dropwise over 1 min and the reaction mixture turned a homogenous yellow colour initially, followed by a appearance of a milky-white precipitate within 3 min stirring. The reaction mixture was further stirred for 1.5 h at room temperature. The reaction mixture was diluted with ether (200 mL) and water (100 mL) and stirred for 15 min at 0 °C. Then a white precipitate was observed. The white solid was isolated by suction filtration and washed with ether (100 mL). The resulting solid was dissolved in boiling methanol (300 mL) and the solution cooled to room temperature overnight. The recrystallised solid was collected using suction filtration and washed with cold methanol (20 mL) and ether (50 mL) to provide the pure N,N'-*ditosylhydrazine* **153** (16.36 g, 96%) as colourless needles; m.p. 210 °C (lit.,[144] 209 °C); ν_{max}/cm^{-1} (KBr) 3437, 3231, 3207, 1598, 1474, 1331, 1187, 1166, 1089, 814, 705, 694; δ_H (300 MHz, DMSO-d_6) 2.40 [3H, s, C<u>H</u>$_3$], 7.38 [2H, d, *J* 8.1, 2 × aromatic <u>H</u>], 7.64 [2H, d, *J* 8.1, 2 × aromatic <u>H</u>], 9.56 [1H, s, N<u>H</u>]. Infrared analysis was consistent with values by Fukuyama.[144] However, it should be noted that the ^{1}H NMR shifts obtained in this work differ significantly from those described by Fukuyama *et al.*[144] but were in excellent agreement with data reported by Grehn and co-workers.[159]

* ^{1}H NMR data reported by Fukuyama;[144] δ_H (400 MHz, DMSO-d_6) 1.56 [3H, s, C<u>H</u>$_3$], 6.54 [2H, d, *J* 8.2, 2 × aromatic <u>H</u>], 6.80 [2H, d, *J* 8.2, 2 × aromatic <u>H</u>], 8.73 [1H, s, N<u>H</u>].

2-Diazo-5-phenylhexan-3-one 204[6,10,11,15,17,167]

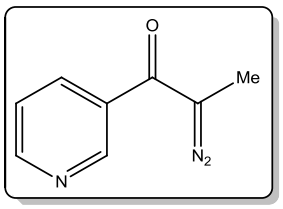


This optimised procedure follows that outlined by Ford,[167] which is a modification of Taber's method.[168] Neat DBU (0.7 mL, 4.85 mmol) was added dropwise to a stirring solution of β-diketone **190** (1.36 g, 4.85 mmol) in dichloromethane (10 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C followed by dropwise addition of a solution of *p*-

nitrobenzenesulfonyl azide **166** (*p*-NBSA) (1.02 g, 4.85 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 1 h at 0 °C. Acetonitrile (5 mL) and ~9.3 g of silica were added to the crude mixture and subsequently concentrated under reduced pressure to give a pale yellow powder. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazoketone* **204** (0.37 g, 38%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2964, 2071, 1714, 1630, 1494, 1367, 701; δ_H (400 MHz, $CDCl_3$) 1.31 [3H, d, *J* 6.8, C(5)HC$\underline{H}_3$], 1.82–2.02 [3H, m contains br s at 1.88 and br s at 1.97, $CN_2C(1)\underline{H}_3$], 2.62–2.77 [2H, m, C(4)$\underline{H}_2$], 3.28–3.42 [1H, m, C(5)$\underline{H}CH_3$], 7.18–7.31 [5H, m, 5 × aromatic $\underline{H}$].** Spectral properties were consistent with previously reported data.[6,10,11,15,17,167]

* Multiplet encompasses signals from both rotamers.
** Sample contains residual *p*-NBSA **166** observed as doublets at δ_H 8.17 and 8.46 ppm.

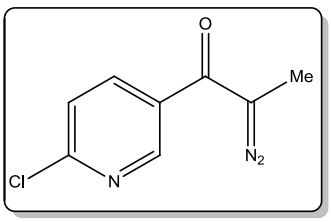
2-Diazo-3-(pyridin-3-yl)propan-3-one 25[32]



A solution of nicotinoyl chloride **27** (5.10 g, 36.02 mmol) in tetrahydrofuran (40 mL) was added dropwise over 1 h to an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (29.53 g, 252 mmol)], while stirring in a salt-ice bath. The solution was then allowed to slowly return to room temperature over 3 h. The ether and residual diazoethane were evaporated under reduced pressure at *ca.* 15 °C, using a rotary evaporator fitted with an acetic acid trap. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazoketone* **25** (2.60 g, 13%) after repeated chromatography as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2928, 2078, 1605, 1417, 1355, 1000, 721; δ_H (300 MHz, $CDCl_3$) 2.08–2.23 [3H, m contains br s at 2.14 (~10%) and br s at 2.18, $CN_2C(1)\underline{H}_3$], 7.40 [1H, dd, *J* 7.8, 4.8, C(5')$\underline{H}$], 7.90 [1H, dt, *J* 7.8, 2.1, C(4')$\underline{H}$], 8.73 [1H, dd, *J* 4.8, 1.5, C(6')$\underline{H}$], 8.83 [1H, d, *J* 1.8, C(2')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 9.4 [CH_3, br, $CN_2\underline{C}(1)H_3$], 63.9 [C, br, $\underline{C}(2)N_2CH_3$], 123.5 [CH, $\underline{C}$(5')H], 133.3 [C, $\underline{C}$(3')], 134.9 [CH, $\underline{C}$(4')H], 148.0 [CH, $\underline{C}$(6')H], 152.0 [CH, $\underline{C}$(2')H], 187.4 [C, br, $\underline{C}$(3)=O].

3-(6-Chloropyridin-3-yl)-2-diazopropan-3-one 63

Method A: Diazoethane acylation



This was prepared following the procedure described for **25**, from a solution of 6-chloronicotinoyl chloride (3.50 g, 19.88 mmol) in tetrahydrofuran (40 mL), an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (16.30 g, 132 mmol)] to yield the crude *diazoketone* as a viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **63** (1.74 g, 45%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2077, 1604, 1583, 1455, 1361, 1105, 998; δ_H (400 MHz, $CDCl_3$) 2.17 [3H, br s, $CN_2C(1)\underline{H}_3$], 7.42 [1H, d, *J* 8.4, C(5')$\underline{H}$], 7.87 [1H, dd, *J* 8.0, 2.4, C(4')$\underline{H}$], 8.61 [1H, d, *J* 2.4, C(2')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 9.3 [CH_3, br, $CN_2\underline{C}(1)H_3$], 63.9 [C, br, $\underline{C}(2)N_2CH_3$], 124.4 [CH, $\underline{C}$(5')H], 132.0 [C, $\underline{C}$(3')], 137.6 [CH, $\underline{C}$(4')H], 148.1 [CH, $\underline{C}$(2')H], 153.8 [C, $\underline{C}$(6')Cl], 185.8 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated from $C_8H_7{}^{37}ClNO$ $[(M+H)–N_2]^+$, 170.0186. Found 170.0194 and exact mass calculated for

$C_8H_7{}^{35}ClNO$ $[(M+H)–N_2]^+$, 168.0216. Found 168.0218. m/z (ES+) 198.0 {$[(C_8H_7{}^{37}ClN_3O)^+]$, 30%}, 196.0 {$[(C_8H_7{}^{35}ClN_3O)^+]$, 74%}, 168.0 {$[(C_8H_7{}^{35}ClN_3O–N_2)^+]$, 10%}.

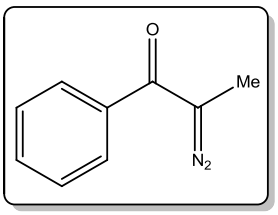
Single crystals of 3-(6-chloropyridin-3-yl)-2-diazopropan-3-one **63** were grown from deuterated chloroform**.** Crystal data: $C_8H_6ClN_3O$, M = 195.61, monoclinic, $P2_1$, a = 6.8928(8) Å, b = 9.9003(12) Å, c = 6.9862(8) Å, β = 118.607(2), V = 418.55(9) Å^3, Z = 2, D_c = 1.552 g cm^{-3}, F_{000} = 200, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 25.07°, μ = 0.413 mm^{-1}, 8697 reflections collected, 1497 unique (R_{int} = 0.0385), final GooF = 1.060, R_1 = 0.0339, wR_2 = 0.0903 (1453 obs. data: $I > 2\sigma(I)$); R_1 = 0.0347, wR_2 = 0.0909 (all data). Full details are given in *Appendix III*.

Method B: Attempted preparation by diazo transfer[167]

A solution of β-diketone **191** (0.67 g, 2.46 mmol) in tetrahydrofuran (10 mL) was added dropwise to a mixture of sodium hydride (60% in mineral oil, 0.06 g, 2.46 mmol) in tetrahydrofuran (10 mL) at 0 °C. A solution of *p*-NBSA **166** (0.56 g, 2.46 mmol) in tetrahydrofuran (10 mL) was added dropwise to the reaction mixture and this was stirred for 1 h at 0 °C. Acetonitrile (5 mL) and ~9.3 g of silica were added to the crude mixture and subsequently concentrated under reduced pressure to give a pale yellow powder. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (1:99) and increased incrementally to ethyl acetate/hexane (5:95) to give a bright yellow oil tentatively assigned as 2-diazo-1-phenylpropan-1-one **205**. The spectral details for this compound are described below.

Major product isolated from method B: Attempted preparation by diazo transfer

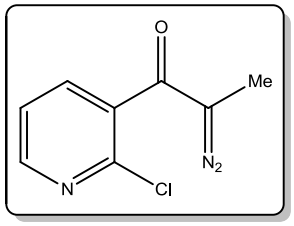
2-Diazo-1-phenylpropan-1-one 205[209]



Bright yellow oil (0.10 g, 21%); ν_{max}/cm^{-1} (film) 2924, 2135, 2074, 1606, 1534, 1348, 1175; δ_H (400 MHz, $CDCl_3$)* 2.15 [CH_3, br s, $CN_2C(1)\underline{H}_3$], 7.38–7.60 [5H, m, 5 × aromatic $\underline{H}$]. Spectral properties were consistent with previously reported data.[209]

* Sample contains residual *p*-NBSA **166**.

3-(2-Chloropyridin-3-yl)-2-diazopropan-3-one 64

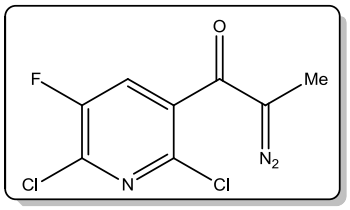


This was prepared following the procedure described for **25**, from a solution of 2-chloronicotinoyl chloride **56** (2.84 g, 16.13 mmol) in tetrahydrofuran (40 mL) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (13.22 g, 113 mmol)] to afford the crude *diazoketone* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazoketone* **64** (0.87 g, 28%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2082, 1607, 1399, 1357, 1083, 998; δ_H (300 MHz, $CDCl_3$) 1.94–2.24 [3H, m contains br s at

2.01 (~10%) and br s at 2.16, $CN_2C(1)\underline{H}_3$], 7.36 [1H, dd, *J* 7.2, 4.8, C(5')H], 7.65–7.78 [1H, m contains d at 7.68 *J* 6.8 (~10%) and d at 7.75 *J* 7.2, C(4')H], 8.48 [1H, d with further unresolved splitting, *J* 4.4, C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 8.3 [CH_3, $CN_2\underline{C}(1)H_3$], 66.3 [C, $\underline{C}(2)N_2CH_3$], 122.6 [CH, C(5')H], 133.7 [C, C(3')], 137.8 [CH, C(4')H], 147.1 [C, C(2')Cl], 151.0 [CH, C(6')H], 186.1 [C, C(3)=O]; HRMS (ES+): Exact mass calculated for $C_8H_7{}^{37}ClNO$ $[(M+H)–N_2]^+$, 170.0186. Found 170.0179 and exact mass calculated for $C_8H_7{}^{35}ClNO$ $[(M+H)–N_2]^+$, 168.0216. Found 168.0204. m/z (ES+) 196.0 {$[(C_8H_7{}^{35}ClN_3O)^+]$, 8%}, 168.0 {$[(C_8H_7{}^{35}ClN_3O–N_2)^+]$, 6%}.

2-Diazo-3-(2,6-dichloro-5-fluoropyridin-3-yl)propan-3-one 65

Method A: Diazoethane acylation



This was prepared following the procedure described for **25**, from a solution of 2,6-dichloro-5-fluoronicotinoyl chloride **59** (5.80 g, 25.00 mmol) in tetrahydrofuran (40 mL) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (20.50 g, 175 mmol)] to yield the crude *diazoketone* as an orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **65** (0.87 g, 21%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2081, 1617, 1398; δ_H (400 MHz, $CDCl_3$), 2.00–2.16 [3H, m contains br s at 2.02 (~10%) and br s at 2.14, $CN_2C(1)\underline{H}_3$], 7.45–7.57 [1H, m contains d at 7.48 J_{HF} 6.8 (~10%) and d at 7.55 J_{HF} 6.8, C(4')H]; δ_C (125.8 MHz, $CDCl_3$) 8.4 [CH_3, br, $CN_2\underline{C}(1)H_3$], 66.8 [C, br, $\underline{C}(2)N_2CH_3$], 126.3 [CH, d, $^2J_{CF}$ 12.9, C(4')H], 133.5 [C, d, $^3J_{CF}$ 1.7, C(3')], 139.5 [C, d, $^2J_{CF}$ 12.8, C(6')Cl], 140.2 [C, d, $^4J_{CF}$ 2.2, C(2')Cl], 154.1 [C, d, $^1J_{CF}$ 158.6, C(5')F]*, 183.2 [C, br, C(3)=O]; δ_F (376.5 MHz in proton decoupled mode, $CDCl_3$) 41.6 [1F, s, C(4')F]; HRMS (ES+): Exact mass calculated for $C_8H_5{}^{35}Cl_2FNO$ $[(M+H)–N_2]^+$, 219.9732. Found 219.9728. m/z (ES+) 221.9 {$[(C_8H_5{}^{37}Cl{}^{35}ClFN_3O–N_2)^+]$, 75%}, 219.9 {$[(C_8H_5{}^{35}Cl_2FN_3O–N_2)^+]$, 100%}.

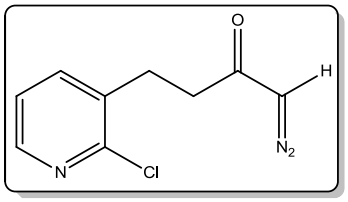
* Intensity of signals for C(5')F was higher than observed for other fluorine-substituted compounds in this work.

Single crystals of 2-diazo-3-(2,6-dichloro-5-fluoropyridin-3-yl)propan-3-one **65** were grown from deuterated chloroform. Crystal data: $C_8H_4Cl_2FN_3O$, M = 248.04, monoclinic, $P2_1/n$, a = 8.529(5) Å, b = 6.704(3) Å, c = 16.826(10) Å, β = 90.766(16)°, V = 962.0(9) Å^3, Z = 4, D_c = 1.713 g cm^{-3}, F_{000} = 496, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 28.43°, μ = 0.663 mm^{-1}, 13029 reflections collected, 2405 unique (R_{int} = 0.0656), final GooF = 1.057, R_1 = 0.0383, wR_2 = 0.0847 (1873 obs. data: $I > 2\sigma(I)$); R_1 = 0.0582, wR_2 = 0.0934 (all data). Full details are given in *Appendix III*.

Method B: Attempted preparation by diazo transfer

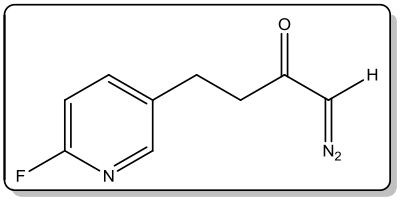
Preparation was attempted following the procedure described for **63** (Method B: Diazo transfer), from sodium hydride (60% in mineral oil, (0.08 g, 3.49 mmol) in tetrahydrofuran (10 mL), β-diketone **195** (1.14 g, 3.49 mmol) in tetrahydrofuran (10 mL) followed by addition of *p*-NBSA **166** (0.80 g, 3.49 mmol) in tetrahydrofuran (10 mL) to give the crude *diazoketone* as a viscous oil/solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (1:99) and increased incrementally to ethyl acetate/hexane (5:95) to give an unknown mixture of products (0.12 g, 14%) as a yellow solid.

4-(2-Chloropyridin-3-yl)-1-diazobutan-2-one 132



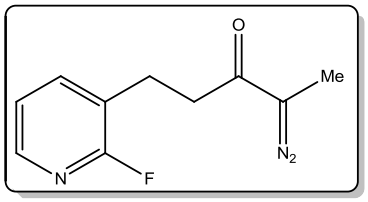
This procedure is based on a method described by Makhey and co-workers.[141] Trimethylsilyldiazomethane **131** (2.0 M in hexanes, 2.6 mL, 5.23 mmol) was added dropwise *via* syringe to a stirring solution of tetrahydrofuran/acetonitrile (20/20 mL) at –20 °C. The reaction vessel was covered with tin foil and stirred for 5 min in a salt-ice bath. A tetrahydrofuran/acetonitrile solution (10/10 mL) of 3-(2-chloropyridin-3-yl)propanoyl chloride **129** (0.53 g, 2.62 mmol) was added dropwise over 30 min to the reaction mixture while stirring in a salt-ice bath. The reaction mixture was then allowed to slowly return to room temperature over 4 h. The ether and residual trimethylsilyldiazomethane were concentrated under reduced pressure at *ca.* 15 °C, using a rotary evaporator fitted with an acetic acid trap. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazoketone* **132** (0.12 g, 22% which is ~80% pure by ^{1}H NMR) as a bright yellow oil; ν_{max}/cm^{-1} (film) 2106, 1638, 1564, 1409, 1378, 1337, 1073; δ_H (300 MHz, $CDCl_3$) 2.67 [2H, br t with unresolved splitting, *J* 6.6, C(3)$\underline{H}_2$], 3.04 [2H, t, *J* 7.2, C(4)$\underline{H}_2$], 5.23 [1H, br s, C(1)$\underline{H}N_2$], 7.15 [1H, dd, *J* 7.5, 4.8, C(5')$\underline{H}$], 7.60 [1H, dd, *J* 7.5, 1.8, C(4')$\underline{H}$], 8.23 [1H, dd, *J* 4.8, 2.8, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 28.1 [CH_2, $\underline{C}$(4)H_2], 39.2 [CH_2, br, $\underline{C}$(3)H_2], 54.8 [CH, br, $\underline{C}$(1)HN_2], 122.6 [CH, $\underline{C}$(5')H], 134.7 [C, $\underline{C}$(3')], 139.5 [CH, $\underline{C}$(4')H], 147.6 [CH, $\underline{C}$(6')H], 151.0 [C, $\underline{C}$(2')Cl], 192.8 [C, $\underline{C}$(2)=O]; HRMS (ES+): Exact mass calculated for $C_9H_9{}^{37}ClNO$ $[(M+H)–N_2]^+$, 184.0343. Found 184.0360 and exact mass calculated for $C_9H_9{}^{35}ClNO$ $[(M+H)–N_2]^+$, 182.0373. Found 182.0372. m/z (ES+) 212.0 {$[(C_9H_9{}^{37}ClN_3O)^+]$, 32%}, 210.0 {$[(C_9H_9{}^{35}ClN_3O)^+]$, 100%}.

1-Diazo-4-(6-fluoropyridin-3-yl)butan-2-one 133



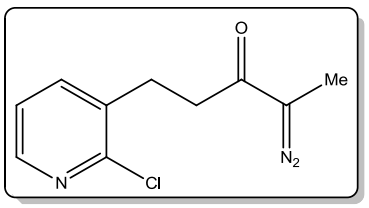
This was prepared following the procedure described for **129**, from a solution of trimethylsilyldiazomethane **131** (2.0 M in hexanes, 4.9 mL, 9.83 mmol) in tetrahydrofuran/acetonitrile (20/20 mL) and a tetrahydrofuran/acetonitrile solution (10/10 mL) of acid chloride **130** (0.92 g, 4.92 mmol) to furnish the crude *diazoketone* as viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **133** (0.18 g, 19%) as a bright yellow oil; ν_{max}/cm^{-1} (film) 2934, 2107, 1637, 1599, 1485, 1396, 1378, 1336, 1249; δ_H (300 MHz, $CDCl_3$) 2.57–2.66 [2H, br m, C(3)$\underline{H}_2$], 2.92 [2H, t, *J* 7.2, C(4)$\underline{H}_2$], 5.27 [1H, br s, C(1)$\underline{H}N_2$], 6.81 [1H, dd, *J* 8.4, 2.7, C(4')$\underline{H}$], 7.61 [1H, ddd, *J* 10.5, 7.8, 2.4, C(5')$\underline{H}$], 8.00 [1H, br d, *J* 2.1, C(2')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 26.4 [CH_2, $\underline{C}$(4)H_2], 40.1 [CH_2, br, $\underline{C}$(3)H_2], 55.2 [CH, br, $\underline{C}$(1)HN_2], 109.0 [CH, d, $^2J_{CF}$ 38.5, $\underline{C}$(5')H], 133.9 [C, d, $^4J_{CF}$ 4.5, $\underline{C}$(3')], 141.2 [CH, d, $^3J_{CF}$ 7.7, $\underline{C}$(4')H], 147.0 [CH, d, $^3J_{CF}$ 14.5, $\underline{C}$(2')H], 162.3 [C, d, $^1J_{CF}$ 237.6, $\underline{C}$(6')F], 196.0 [C, $\underline{C}$(2)=O]; δ_F (376.5 MHz in proton coupled mode, $CDCl_3$) 90.1 [1F, d, *J* 7.6, C(6')$\underline{F}$]; HRMS (ES+): Exact mass calculated for C_9H_9FNO $[(M+H)–N_2]^+$, 166.0651. Found 166.0656. m/z (ES+) 194.1 $[(M+H)^+$, 100%].

2-Diazo-5-(2-fluoropyridin-3-yl)pentan-3-one 138



This procedure is a modification of a method described by Dolenc *et al.* in the preparation of α-diazoketones from unsymmetrical anhydrides and trimethylsilyldiazomethane.[142] Triethylamine (0.9 mL, 6.43 mmol) and a solution ethyl chloroformate (0.6 mL, 6.43 mmol) in tetrahydrofuran (10 mL) were added dropwise sequentially to a tetrahydrofuran solution (30 mL) of acid **105** (1.05 g, 6.23 mmol) while stirring in a salt-ice bath. The reaction mixture was stirred for 30 min in a salt-ice bath. The white precipitate formed was assumed to be triethylamine hydrochloride and was removed by gravity filtration. The solution of mixed anhydride was transferred to a pressure equalised addition funnel and added dropwise over 1 h to an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (5.11 g, 43.60 mmol)], while stirring in a salt-ice bath. The solution was then allowed to slowly return to room temperature over 3 h. The ether and residual diazoethane were evaporated under reduced pressure at *ca.* 15 °C, using a rotary evaporator fitted with an acetic acid trap. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **138** (0.09 g, 7%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2933, 2075, 1746 w, 1630, 1608, 1578, 1438, 1376, 1287, 1244; δ_H (300 MHz, $CDCl_3$) 1.89–2.14 [3H, m, contains br s at 1.94 and br s at 2.07 (~10%), $CN_2C(1)\underline{H}_3$], 2.67–2.88 [2H, m, contains br s at 2.73 (~10%) and br t at 2.81, *J* 7.2, C(4)$\underline{H}_2$], 3.00 [2H, t, *J* 7.5, C(5)$\underline{H}_2$], 7.11 [1H, ddd, *J* 7.2, 5.1, 2.1, C(5')$\underline{H}$], 7.68 [1H, br t, *J* 8.1, C(4')$\underline{H}$], 8.07 [1H, br d with further unresolved splitting, *J* 3.3, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 8.0 [CH_3, $CN_2\underline{C}(1)H_3$], 24.0 [CH_2, $\underline{C}(5)H_2$], 36.8 [CH_2, br, $\underline{C}(4)H_2$], 62.6 [C, br, $\underline{C}(2)N_2CH_3$], 121.5 [CH, d, $^4J_{CF}$ 4.2, $\underline{C}$(5')H], 122.5 [CH, d, $^2J_{CF}$ 28.2, $\underline{C}$(3')], 141.5 [CH, d, $^3J_{CF}$ 5.9, $\underline{C}$(4')H], 145.6 [CH, d, $^3J_{CF}$ 14.7, $\underline{C}$(6')H], 162.0 [C, d, $^1J_{CF}$ 238.5, $\underline{C}$(2')F], 192.4 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}FNO$ $[(M+H)–N_2]^+$, 180.0825. Found 180.0829. m/z (ES+) 221.0 (100%), 208.1 {$[(C_{10}H_{11}FN_3O)^+]$, 6%}, 180.1 {$[(C_{10}H_{11}FN_3O–N_2)^+]$, 44%}.

5-(2-Chloropyridin-3-yl)-2-diazopentan-3-one 134

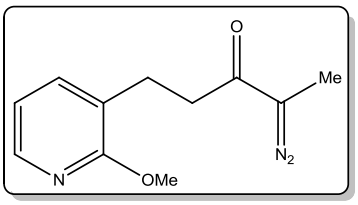


This was prepared following the procedure described for **138**, from a solution of acid **101** (1.15 g, 6.190 mmol) in tetrahydrofuran (30 mL), triethylamine (0.9 mL, 6.40 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.6 mL, 6.40 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (5.08 g, 43.36 mmol)] to generate the crude *diazoketone* as orange oil which is ~10% pure by ^{1}H NMR. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **134** (0.08 g, 6%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2078, 1726 w, 1631, 1563 w, 1409, 1284, 1074, 913, 746; δ_H (400 MHz, $CDCl_3$) 1.92–2.10 [3H, m, contains br s at 1.94 and br s at 2.08 (~10%), $CN_2C(1)\underline{H}_3$], 2.72–2.89 [2H, m, contains br t at 2.75 (~10%) and br t with further unresolved splitting at 2.84, *J* 7.6, C(4)$\underline{H}_2$], 3.08 [2H, t with further unresolved splitting, *J* 7.6, C(5)$\underline{H}_2$], 7.18 [1H, dd, *J* 7.6, 4.8, C(5')$\underline{H}$], 7.60–7.69 [1H, m, C(4')$\underline{H}$], 8.24–8.31 [1H, m, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$)* 8.0 [CH_3, $CN_2\underline{C}(1)H_3$], 28.1 [CH_2, $\underline{C}(5)H_2$], 36.4 [CH_2, br, $\underline{C}(4)H_2$], 62.6 [C, br, $\underline{C}(2)N_2CH_3$], 122.7 [CH, $\underline{C}$(5')H], 134.8 [C, $\underline{C}$(3')], 139.7 [CH, $\underline{C}$(4')H], 147.7 [CH, $\underline{C}$(6')H], 151.1 [C, $\underline{C}$(2')Cl], 192.5 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{37}ClNO$ $[(M+H)–N_2]^+$, 198.0499. Found

198.0517 and exact mass calculated for $C_{10}H_{11}{}^{35}ClNO$ $[(M+H)–N_2]^+$, 196.0529. Found 196.0539. m/z (ES+) 226.0 {$[(C_{10}H_{11}{}^{37}ClN_3O)^+]$, 36%}, 224.0 {$[(C_{10}H_{11}{}^{35}ClN_3O)^+]$, 100%}. A less polar product was isolated as a pale yellow oil (0.30 g, 22%) and the impure sample appeared to contain a mixture of products resembling ester **81**, α-diazoketone **134** and possibly some mixed anhydride.

*^{1}H NMR data above refers to sample of **134** run at 400 MHz while ^{1}H NMR data in **Figure 2.25** is from sample of **134** run at 500 MHz.
** Unidentified quaternary carbon seen at δ_C 68.5 ppm.

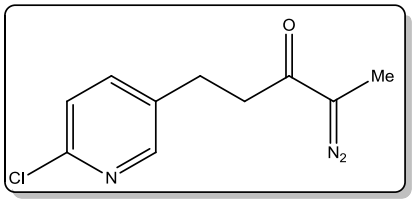
2-Diazo-5-(2-methoxypyridin-3-yl)pentan-3-one 139



This was prepared following the procedure described for **138**, from a solution of acid **106** (0.95 g, 5.24 mmol) in tetrahydrofuran (30 mL), triethylamine (0.8 mL, 5.41 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.5 mL, 5.41 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (4.29 g, 36.66 mmol)] to afford the crude *diazoketone* as a viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazoketone* **139** (0.26 g, 23%) as viscous yellow oil; ν_{max}/cm^{-1} (film) 2952, 2073, 1736 w, 1638, 1594, 1467, 1412, 1313, 1257, 1066, 1022; δ_H (300 MHz, $CDCl_3$) 1.93 [3H, br s, $CN_2C(1)\underline{H}_3$], 2.76 [2H, br t, *J* 7.5, $C(4)\underline{H}_2$], 2.90 [2H, t, *J* 7.2, $C(5)\underline{H}_2$], 3.96 [3H, s, $OC\underline{H}_3$], 6.80 [1H, dd, *J* 7.2, 5.1, C(5')H], 7.41 [1H, br d, *J* 6.6, C(4')H], 8.02 [1H, dd, *J* 5.1, 2.1, C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 8.0 [CH_3, br, $CN_2\underline{C}(1)H_3$], 25.9 [CH_2, br, $\underline{C}(5)H_2$], 36.8 [CH_2, br, $\underline{C}(4)H_2$], 53.2 [CH_3, $O\underline{C}H_3$], 62.3 [C, $\underline{C}(2)N_2CH_3$], 116.7 [CH, $\underline{C}(5')H$], 123.0 [C, $\underline{C}(3')$], 138.3 [CH, $\underline{C}(4')H$], 144.8 [CH, $\underline{C}(6')H$], 162.1 [C, $\underline{C}(2')OCH_3$], 193.8 [C, $\underline{C}(3)$=O]; HRMS (ES+): Exact mass calculated for $C_{11}H_{14}N_3O_2$ $[M+H]^+$, 220.1086. Found 220.1102 and exact mass calculated for $C_{11}H_{14}NO_2$ $[(M+H)–N_2]^+$, 192.1025. Found 192.1026. m/z (ES+) 220.2 {$[(C_{11}H_{14}N_3O_2)^+]$, 100%}, 192.3 {$[(C_{11}H_{14}N_3O_2–N_2)^+]$, 30%}, 132.2 (80%).

5-(6-Chloropyridin-3-yl)-2-diazopentan-3-one 135

Method A: Diazoethane acylation



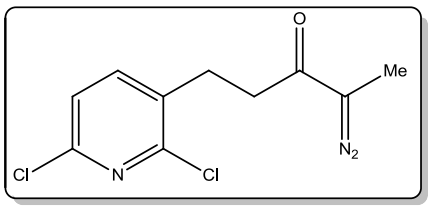
This was prepared following the procedure described for **138**, from a solution of acid **102** (0.58 g, 3.13 mmol) in tetrahydrofuran (30 mL), triethylamine (0.5 mL, 3.23 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.3 mL, 3.23 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (2.57 g, 21.90 mmol)] to yield the crude *diazoketone* as orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **135** (0.09 g, 13%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2932, 2079, 1746 w, 1630, 1460, 1377, 1281, 1107; δ_H (400 MHz, $CDCl_3$) 1.91–2.09 [3H, m, contains br s at 1.94 and br s at 2.06 (~10%), $CN_2C(1)\underline{H}_3$], 2.64–2.84 [2H, m, contains br s at 2.69 (~10%) and br t at 2.78, *J* 7.6, $C(4)\underline{H}_2$], 2.97 [2H, t, *J* 7.6, $C(5)\underline{H}_2$], 7.25 [1H, d, *J* 8.0, C(5')H], 7.52 [1H, br dd, *J* 8.0, 2.0, C(4')H], 8.25 [1H, d, *J* 2.4, C(2')H]; δ_C (75.5 MHz, $CDCl_3$) 8.0 [CH_3, br,

$CN_2\underline{C}(1)H_3$], 26.7 [CH_2, br, $\underline{C}(5)H_2$], 38.4 [CH_2, br, $\underline{C}(4)H_2$], 62.6 [C, br, $\underline{C}(2)N_2CH_3$], 124.0 [CH, $\underline{C}(5')H$], 135.1 [C, $\underline{C}(3')$], 139.1 [CH, $\underline{C}(4')H$], 149.4 [C, $\underline{C}(6')Cl$], 149.6 [CH, $\underline{C}(2')H$], 192.2 [C, $\underline{C}(3)=O$]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{35}ClN_3O$ $[M+H]^+$, 224.0591. Found 224.0580. Exact mass calculated for $C_{10}H_{11}{}^{37}ClNO$ $[(M+H)–N_2]^+$, 198.0499. Found 198.0518 and exact mass calculated for $C_{10}H_{11}{}^{35}ClNO$ $[(M+H)–N_2]^+$, 196.0528. Found 196.0538. m/z (ES+) 267.0 (14%), 265.0 (36%), 226.0 {$[(C_{10}H_{11}{}^{37}ClN_3O)^+]$, 35%}, 224.0 {$[C_{10}H_{11}{}^{35}ClN_3O)^+]$, 100%}. A less polar product identified as ethyl 3-(6-chloropyridin-3-yl)propanoate **93** (0.36 g, 52%) was isolated as a pale yellow oil. Spectral properties for **93** were in agreement with those described previously in this work.

Method B: Diazo transfer

A solution of *p*-NBSA **166** (0.31 g, 1.36 mmol) in tetrahydrofuran (10 mL) was added dropwise to a stirring suspension of sodium hydride (0.05 g, 60% mineral dispersion, 1.36 mmol) in tetrahydrofuran (10 mL) and solution (10 mL) of β-diketone **196** (0.41 g, 1.36 mmol) in tetrahydrofuran (10 mL).The reaction mixture was stirred for 1 h at 0 °C and the reaction progress monitored by TLC analysis and infrared spectroscopy.The reaction was deemed to be complete after 1 h and evaporation of excess solvent under reduced pressure gave the crude *diazoketone* as a viscous yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (30:70) afforded the pure *α-diazoketone* **135** (0.09 g, 30%); ν_{max}/cm^{-1} (film) 2919, 2075, 1630, 1560, 1459, 1376, 1281, 1106; δ_H (400 MHz, $CDCl_3$) 1.89–2.11 [3H, m, contains br s at 1.93 and br s at 2.03 (~10%), $CN_2C(1)\underline{H}_3$], 2.62–2.82 [2H, m, contains br s at 2.69 (~10%) and br t at 2.76, *J* 7.2, $C(4)\underline{H}_2$], 2.96 [2H, t, *J* 7.2, $C(5)\underline{H}_2$], 7.23 [1H, d, *J* 8.0, $C(5')\underline{H}$], 7.51 [1H, br dd, *J* 8.4, 1.6, $C(4')\underline{H}$], 8.23 [1H, d, *J* 2.0, $C(2')\underline{H}$].

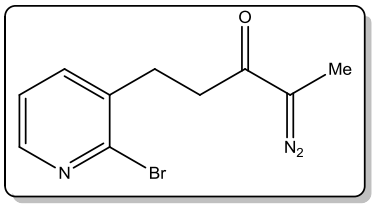
2-Diazo-5-(2,6-dichloropyridin-3-yl)pentan-3-one 136



This was prepared following the procedure described for **138**, from a solution of acid **103** (0.41 g, 1.85 mmol) in tetrahydrofuran (30 mL), triethylamine (0.3 mL, 1.91 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.2 mL, 1.91 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (1.52 g, 12.96 mmol)] to provide the crude *diazoketone* as orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *α-diazoketone* **136** (0.02 g, 4%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2923, 2068, 1627, 1550, 1426; δ_H (400 MHz, $CDCl_3$) 1.89–2.13 [3H, m, contains br s at 1.94 and br s at 2.07 (~10%), $CN_2C(1)\underline{H}_3$], 2.68–2.88 [2H, m, contains br s at 2.74 (~10%) and br t at 2.82, *J* 7.2, $C(4)\underline{H}_2$], 3.06 [2H, t, *J* 7.2, $C(5)\underline{H}_2$], 7.20 [1H, d, *J* 8.0 $C(5')\underline{H}$], 7.62 [1H, br d, *J* 8.0, $C(4')\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 8.0 [CH_3, br, $CN_2\underline{C}(1)H_3$], 27.3 [CH_2, br, $\underline{C}(5)H_2$], 36.1 [CH_2, br, $\underline{C}(4)H_2$], 62.7 [C, $\underline{C}(2)N_2CH_3$], 123.1 [CH, $\underline{C}(5')H$], 133.7 [C, $\underline{C}(3')$], 142.1 [CH, br, $\underline{C}(4')H$], 148.2 [C, $\underline{C}(2')Cl$ or $\underline{C}(6')Cl$], 149.8 [C, $\underline{C}(2')Cl$ or $\underline{C}(6')Cl$], 192.1 [C, $\underline{C}(3)=O$]; HRMS (ES+): Exact mass calculated for $C_{10}H_{10}{}^{37}Cl^{35}ClNO$ $[(M+H)–N_2]^+$, 232.0110. Found 232.0104 and exact mass calculated for $C_{10}H_{10}{}^{35}Cl_2NO$ $[(M+H)–N_2]^+$, 230.0139. Found 230.0129. m/z (ES+) 260.0 {$[(C_{10}H_{10}{}^{37}Cl^{35}ClN_3O)^+]$, 28%}, 258.0 {$[(C_{10}H_{10}{}^{35}Cl_2N_3O)^+]$, 38%}, 232.0 {$[(C_{10}H_{10}{}^{37}Cl^{35}ClN_3O–N_2)^+]$, 22%}, 230.0 {$[(C_{10}H_{10}{}^{35}Cl_2N_3O–N_2)^+]$, 34%}, 191.0 (100%), 161.0 (23%).

* Unidentified C–H in the ^{13}C NMR spectrum seen at δ_C 34.8 ppm.

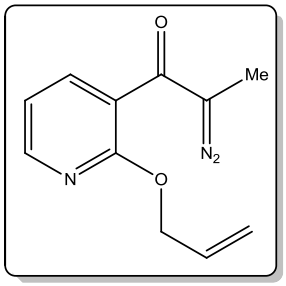
5-(2-Bromopyridin-3-yl)-2-diazopentan-3-one 137



This was prepared following the procedure described for **138**, from a solution of acid **104** (1.65 g, 6.19 mmol) in tetrahydrofuran (30 mL), triethylamine (0.7 mL, 7.40 mmol), a tetrahdrofuran solution (10 mL) of ethyl chloroformate (0.7 mL, 7.40 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (5.87 g, 50.16 mmol)] to afford the crude *diazoketone* as a viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (15:85) gave the pure *α-diazoketone* **137** (0.58 g, 30%) as viscous yellow oil; ν_{max}/cm^{-1} (film) 2931, 2078, 1746 w, 1631, 1559, 1404, 1373, 1283, 1050; δ_H (300 MHz, $CDCl_3$)* 1.90–2.13 [3H, m, contains br s at 1.94 and br s at 2.08 (~10%), $CN_2C(1)\underline{H}_3$], 2.70–2.91 [2H, m, contains br s at 2.76 (~10%) and br t at 2.84, *J* 7.2, $C(4)\underline{H}_2$], 3.08 [2H, t, *J* 7.5, $C(5)\underline{H}_2$], 7.21 [1H, dd, *J* 7.5, 4.8, C(5')H], 7.60 [1H, br d, *J* 6.9, C(4')H], 8.23 [1H, dd, *J* 4.8, 2.1, C(6')H]; δ_C (75.5 MHz, $CDCl_3$)** 8.0 [CH_3, br, $CN_2\underline{C}(1)H_3$], 30.1 [CH_2, br, $\underline{C}(5)H_2$], 36.6 [CH_2, br, $\underline{C}(4)H_2$], 62.6 [C, br, $\underline{C}(2)N_2CH_3$], 122.9 [CH, $\underline{C}$(5')H], 137.3 [C, br, $\underline{C}$(3')], 139.1 [CH, br, $\underline{C}$(4')H], 144.0 [C, $\underline{C}$(2')Br], 148.0 [CH, $\underline{C}$(6')H], 192.3 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{81}BrN_3O$ $[M+H]^+$, 270.0065. Found 270.0067 and exact mass calculated for $C_{10}H_{11}{}^{79}BrN_3O$ $[M+H]^+$, 268.0085. Found 268.0084. m/z (ES+) 242.2 {$[(C_{10}H_{11}{}^{81}BrN_3O–N_2)^+]$, 99%}, 240.2 {$[(C_{10}H_{11}{}^{79}BrN_3O–N_2)^+]$, 100%}.

* Residual ethyl acetate in analysed sample.
** Unidentified C–H in the ^{13}C NMR spectrum at δ_C 129.6 ppm as confirmed by DEPT 90/DEPT 135 experiments.

3-[2-(Allyloxy)pyridin-3-yl]-2-diazopropan-3-one 140

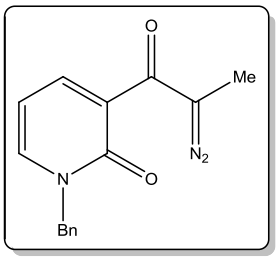


This was prepared following the procedure described for **138**, from a solution of acid **117** (3.00 g, 16.74 mmol) in tetrahydrofuran (30 mL), triethylamine (2.4 mL, 17.30 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (1.7 mL, 17.30 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (13.72 g, 43.60 mmol)] to yield the crude *diazoketone* as a viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (30:70) with subsequent chromatography using dichloromethane (100:0) to dichloromethane/methanol (95:5) gave the pure *α-diazoketone* **140** (0.40 g, 30%) as viscous yellow oil; ν_{max}/cm^{-1} (film) 2931, 2078, 1752, 1604, 1590, 1431, 1415, 1354, 1289, 1246, 1105, 991; δ_H (400 MHz, $CDCl_3$) 2.11 [3H, br s, $CN_2C(1)\underline{H}_3$], 4.91 [2H, dt, *J* 5.2, 1.6, $OC\underline{H}_2CHCH_2$], 5.25 [1H, dd with further unresolved splitting, *J* 10.4, 1.2, one of $OCH_2CHC\underline{H}_2$], 5.39 [1H, dd with further unresolved splitting, *J* 17.2, 1.6, one of $OCH_2CHC\underline{H}_2$], 6.02–6.15 [1H, m, $OCH_2C\underline{H}CH_2$], 6.97 [1H, dd, *J* 7.2, 4.8, C(5')H], 7.75 [1H, br d, *J* 6.8, C(4')H], 8.23 [1H, dd, *J* 5.2, 2.0, C(6')H]; δ_C (125.8 MHz, $CDCl_3$) 8.8 [CH_3, br, $CN_2\underline{C}(1)H_3$], 65.5 [C, br, $\underline{C}(2)N_2CH_3$], 67.1 [CH_2, $O\underline{C}H_2CHCH_2$], 117.1 [CH, $\underline{C}$(5')H], 117.6 [CH_2, $OCH_2CH\underline{C}H_2$], 121.9 [C, br, $\underline{C}$(3')], 133.0 [CH, $OCH_2\underline{C}HCH_2$], 139.1 [CH, br, $\underline{C}$(4')H], 149.2 [CH, $\underline{C}$(6')H], 159.1 [C, $\underline{C}(2')OCH_2CHCH_2$],

187.2 [C, br, C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NO_2$ $[(M+H)–N_2]^+$, 190.0868. Found 190.0864 {$[(C_{11}H_{12}N_3O_2–N_2)^+]$, 100%}. m/z (ES+) 190.3 {$[(C_{11}H_{12}N_3O_2–N_2)^+]$, 100%}.

1-Benzyl-3-(2-diazopropanoyl)pyridin-2(1*H*)-one 141

Method A: Diazoethane acylation

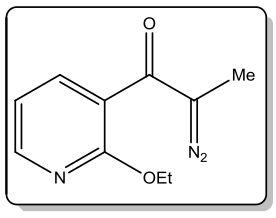


This was prepared following the procedure described for **138**, from acid **122** (2.00 g, 8.72 mmol) dissolved in tetrahydrofuran (30 mL), triethylamine (1.3 mL, 9.00 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.9 mL, 9.00 mmol) followed by addition to an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (7.15 g, 61.07 mmol)] to yield the crude *diazoketone* as a viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (30:70) with subsequent chromatography using dichloromethane/methanol (100:0) to (95:5) to afford the pure *α-diazoketone* **141** (0.56 g, 24%) as a viscous yellow oil which later solidified; ν_{max}/cm^{-1} (film) 2929, 2081, 1736, 1654, 1585, 1546, 1458, 1353, 1017; δ_H (400 MHz, $CDCl_3$) 2.08 [3H, br s, $CN_2C(1)\underline{H}_3$], 5.16 [2H, s, $NC\underline{H}_2C_6H_5$], 6.24 [1H, dd, *J* 6.8, 6.8, C(5')H], 7.26–7.38 [5H, m, 5 × aromatic H], 7.45 [1H, dd, *J* 6.8, 2.0, C(4')H], 7.72 [1H, br d, *J* 6.0, C(6')H]; HRMS (ES+): Exact mass calculated for $C_{15}H_{14}NO_2$ $[(M+H)–N_2]^+$, 240.1025. Found 240.1016. m/z (ES+) 240.3 {$[(C_{15}H_{14}N_3O_2–N_2)^+]$, 54%}.

Method B: Diazo transfer

This was prepared following the procedure for **63** (Method B: Diazo transfer) with a modification involving 2.0 equiv. of both *p*-NBSA **166** and sodium hydride employed in this case, from a suspension of sodium hydride (0.07 g, 60% in mineral oil, 2.91 mmol) in tetrahydrofuran (10 mL), β-diketone **200** (0.50 g, 1.46 mmol) dissolved in tetrahydrofuran (10 mL) stirring at 0 °C and a solution (10 mL) of *p*-NBSA **166** (0.67 g, 2.91 mmol) in tetrahydrofuran (10 mL). The reaction was found to be complete after warming to room temperature overnight as determined by TLC analysis. Purification by flash chromatography on silica gel eluted with ethyl acetate/hexane (20:80) to (30:70) to (60:40) furnished the pure *α-diazoketone* **141** (0.04 g, 11%) as a bright yellow oil; ν_{max}/cm^{-1} (film) 2082, 1652, 1583, 1549, 1456, 1353; δ_H (300 MHz, $CDCl_3$) 2.09 [3H, br s, $CN_2C(1)\underline{H}_3$], 5.17 [2H, br s, $NC\underline{H}_2C_6H_5$], 6.25 [1H, dd, *J* 6.9, 6.9, C(5')H], 7.25–7.40 [5H, m, 5 × aromatic H], 7.45 [1H, dd, *J* 6.6, 2.1, C(4')H], 7.73 [1H, br d, *J* 5.7, C(6')H]; δ_C (150.9 MHz, $CDCl_3$) 9.4 [CH_3, br, $CN_2C(1)H_3$], 52.6 [CH_2, $NCH_2C_6H_5$], 65.9 [C, br, $C(2)N_2CH_3$], 105.9 [CH, C(5')H], 128.3 [CH, 2 × aromatic CH], 128.4 [CH, aromatic CH], 129.2 [CH, 2 × aromatic CH], 130.3 [C, C(3')], 135.8 [C, aromatic C], 140.4 [CH, br, C(4')H or C(6')H], 142.3 [CH, br, C(4)H or C(6')H], 159.0 [C, C(2')=O], 186.5 [C, br, C(3)=O].

2-Diazo-1-(2-ethoxypyridin-3-yl)propan-1-one 142



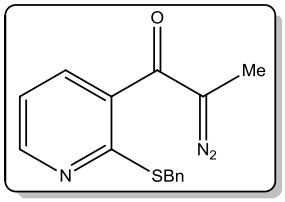
This was prepared following the procedure described for **138**, from a solution of acid **124** (2.50 g, 14.95 mmol) in tetrahydrofuran (30 mL), triethylamine (2.2 mL, 15.44 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (1.5 mL, 15.44 mmol) and an ethereal

solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (12.26 g, 105 mmol)] to yield the crude *diazoketone* as viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) with repeated chromatography to afford the pure *α-diazoketone* **142*** (0.06 g, 7%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2984, 2084, 1772, 1611, 1594, 1571, 1370, 1211; δ_H (400 MHz, $CDCl_3$) 1.36 [3H, t, *J* 7.2, $OCH_2C\underline{H}_3$], 2.09 [3H, br s, $CN_2C(1)\underline{H}_3$], 4.32 [2H, q, *J* 7.2, $OC\underline{H}_2CH_3$], 7.32 [1H, dd, *J* 7.6, 4.8, C(5')H], 7.86 [1H, br d, *J* 7.2, C(4')H], 8.46 [1H, dd, *J* 4.8, 2.0, C(6')H]; HRMS (ES+): Exact mass calculated for $C_{10}H_{12}NO_2$ $[(M+H)–N_2]^+$, 178.0868. Found 178.0863 $[(C_{10}H_{12}N_3O_2–N_2)^+]$. m/z (ES+) 178.3 $\{[(C_{10}H_{12}N_3O_2–N_2)^+]$, 28%}.

* α-Diazoketone **142** assigned as *O*-ethyl tautomer by comparison with spectroscopic signals reported for *N*-alkylated α-diazoketones **141** and **207** elsewhere in this work. The acid starting material was identified as the *N*-ethyl acid **124**; however, this may have converted to the *O*-ethyl tautomer **123** prior to diazoethane acylation, although this is merely speculative.

3-[2-(Benzylthio)pyridin-3-yl]-2-diazopropan-3-one 143

Method A: Diazoethane acylation



This was prepared following the procedure described for **138**, from a solution of acid **127** (1.86 g, 7.57 mmol) in tetrahydrofuran (30 mL), triethylamine (1.1 mL, 7.82 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.8 mL, 7.82 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (6.21 g, 53.0 mmol)] to give the crude *diazoketone* as viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (15:85) to (20:80) to (30:70) furnished the pure *α-diazoketone* **143** (0.50 g, 23%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2078, 1751, 1604, 1573, 1552, 1496, 1453, 1393, 1346; δ_H (400 MHz, $CDCl_3$) 2.07 [3H, br s, $CN_2C(1)\underline{H}_3$], 4.48 [2H, s, $SC\underline{H}_2C_6H_5$], 7.06 [1H, dd, *J* 7.6, 4.8, C(5')H], 7.20–7.32 [3H, m, 3 × aromatic H], 7.40 [2H, d, *J* 8.8, 2 × aromatic H], 7.51 [1H, dd, *J* 7.6, 1.2, C(4')H], 8.51 [1H, dd, *J* 4.8, 2.0, C(6')H]; δ_C (125.8 MHz, $CDCl_3$)* 8.7 [CH_3, br, $CN_2\underline{C}(1)H_3$], 34.5 [CH_2, $S\underline{C}H_2C_6H_5$], 65.6 [C, $\underline{C}(2)N_2CH_3$], 119.0 [CH, $\underline{C}(5')H$], 127.2 [CH, aromatic CH], 128.4 [CH, 2 × aromatic CH], 129.2 [CH, 2 × aromatic CH], 132.0 [C, br, $\underline{C}(3')$], 134.8 [CH, $\underline{C}(4')H$], 137.5 [C, aromatic C] 150.4 [CH, $\underline{C}(6')H$], 156.4 [C, $\underline{C}(2')SCH_2C_6H_5$]; HRMS (ES+): Exact mass calculated for $C_{15}H_{14}N_3OS$ $[M+H]^+$, 284.0858. Found 284.0853 $\{[(C_{15}H_{14}N_3OS)^+]$, 100%} and exact mass calculated for $C_{15}H_{14}NOS$ $[(M+H)–N_2]^+$, 256.0796. Found 256.0789 $\{[(C_{15}H_4N_3OS–N_2)^+]$, 49%}. m/z (ES+) 284.3 $\{[(C_{15}H_{14}N_3OS)^+]$, 100%}, 256.3 $\{[(C_{15}H_{14}N_3OS–N_2)^+]$, 34%}.

* Signal for $\underline{C}(3)$=O not detected.

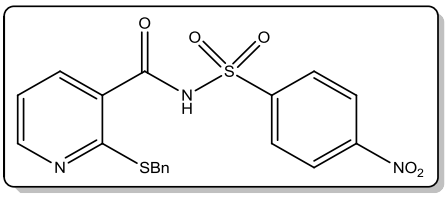
Method B: Attempted diazo transfer reaction

Preparation was attempted following the procedure for **63** (Method B: Diazo Transfer)**,** from a suspension of sodium hydride (0.03 g, 60% mineral dispersion, 1.06 mmol) in tetrahydrofuran (10 mL), β-diketone **197** (0.38 g, 1.06 mmol) dissolved in tetrahydrofuran (10 mL) stirring at 0 °C and a solution (10 mL) of *p*-NBSA **166** (0.24 g, 2.91 mmol) in tetrahydrofuran (10 mL). The reaction was found to be complete after warming to room temperature overnight as determined by TLC analysis. Purification after repeated flash

chromatography on silica gel eluted with ethyl acetate/hexane (20:80) to (30:70) furnished a bright yellow oil (0.02 g, 6%) **143** which was found to co-elute with the *1,3-diketone* **197** as the less polar fraction (1.19 : 1.0 of **197** : **143**) and a white solid **208** (0.03 g, 9%) as the more polar fraction. ^{1}H NMR and IR signals for the yellow oil indicate formation of α-diazoketone **97** by comparison with method A but this material was not isolated cleanly. The signals for the white solid led to the tentative assignment of sulfonamide **208**. The spectral details for this compound are described below.

Major product isolated from Method B: Attempted preparation using diazo transfer

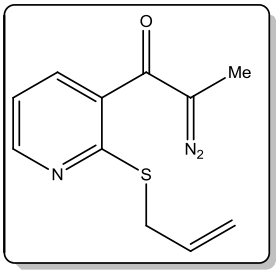
2-(Benzylthio)-*N*-[(4-nitrophenyl)sulfonyl]nicotinamide 208



Unknown A **208**, white solid (0.03 g) (more polar fraction); ν_{max}/cm^{-1} (film) 3369, 2935, 1655 w, 1534, 1391, 1196, 1109; δ_H (400 MHz, $CDCl_3$)* 4.39 [2H, s, $SC\underline{H}_2C_6H_5$], 7.12 [1H, dd, *J* 7.2, 4.8, C(5')H], 7.25–7.33 [5H, m, 5 × aromatic H], 7.49 [1H, dd, *J* 7.6, 2.0, C(4")H], 8.18 [2H, d with further unresolved splitting, *J* 9.2, 2 × aromatic H], 8.23 [2H, d with further unresolved splitting, *J* 8.8, 2 × aromatic H], 8.57 [1H, dd, *J* 4.8, 1.6, C(6")H].

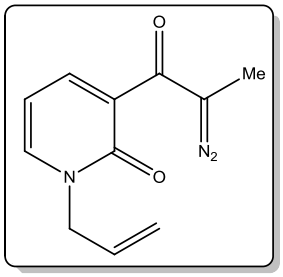
* Unknown signal seen at δ_H 2.27 ppm [3H, s].

3-[2-(Allylthio)pyridin-3-yl]-2-diazopropan-3-one 144



This was prepared following the procedure described for **138**, from a solution of acid **125** (1.70 g, 8.71 mmol) in tetrahydrofuran (30 mL), triethylamine (1.3 mL, 9.00 mmol), a tetrahydrofuran solution (10 mL) of ethyl chloroformate (0.9 mL, 9.00 mmol) and an ethereal solution of diazoethane **20** [prepared from *N*-ethyl-*N*-nitrosourea **62** (7.14 g, 61.0 mmol)] to provide the crude *diazoketone* as viscous orange oil. Repeated purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) furnished the pure *α-diazoketone* **144** (0.08 g, 4%) as a viscous yellow oil; ν_{max}/cm^{-1} (film) 2982, 2080, 1749, 1664, 1607, 1576, 1552, 1394, 1135; δ_H (400 MHz, $CDCl_3$) 2.10 [3H, br s, $CN_2C(1)\underline{H}_3$], 3.89 [2H, dt, *J* 7.2, 1.2, $SC\underline{H}_2CHCH_2$], 5.09 [1H, dd with further unresolved splitting, *J* 10.0, 1.6, one of $SCH_2CHC\underline{H}_2$], 5.28 [1H, dd with further unresolved splitting, *J* 17.2, 1.2, one of $SCH_2CHC\underline{H}_2$], 5.89–5.99 [1H, m, $SCH_2C\underline{H}CH_2$], 7.04 [1H, dd, *J* 7.2, 4.8, C(5')H], 7.50 [1H, dd, *J* 7.6, 2.0, C(4')H], 8.50 [1H, dd, *J* 4.8, 1.6, C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 8.7 [CH_3, br, $CN_2\underline{C}(1)H_3$], 32.8 [CH_2, $S\underline{C}H_2CHCH_2$], 65.6 [C, br, $\underline{C}(2)N_2CH_3$], 117.8 [CH_2, $SCH_2CH\underline{C}H_2$], 118.9 [CH, C(5')H], 132.3 [C, C(3')], 133.5 [CH, C(4')H or $SCH_2\underline{C}HCH_2$], 134.6 [CH, C(4')H] or C(2')$SCH_2\underline{C}HCH_2$], 150.3 [CH, C(6')H], 155.9 [C, C(2')SCH_2CHCH_2], no signal for C=O detected; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}N_3OS$ $[M+H]^+$, 234.0701. Found 234.0685 and exact mass calculated for $C_{11}H_{12}NOS$ $[(M+H)–N_2]^+$, 206.0623. Found 206.0619. m/z (ES+) 234.3 {$[(C_{11}H_{12}N_3OS)^+]$, 100%}, 206.3 {$[(C_{11}H_{12}N_3OS–N_2)^+]$, 30%}.

1-Allyl-3-(2-diazopropanoyl)pyridin-2(1*H*)-one 207

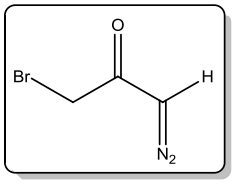


This was prepared following the procedure for **63** (Method B: Diazo transfer)**,** from a suspension of sodium hydride (0.03 g, 60% mineral dispersion, 1.06 mmol) in tetrahydrofuran (10 mL), β-diketone **199** (0.31 g, 1.06 mmol) dissolved in tetrahydrofuran (10 mL) stirring at 0 °C and a tetrahydrofuran solution (10 mL) of *p*-NBSA **166** (0.24 g, 1.06 mmol). The reaction was found to be complete after 1 h as determined by TLC analysis. Purification by flash chromatography on silica gel eluted with ethyl acetate/hexane (30:70) furnished the pure *α-diazoketone* **207** (0.10 g, 43%) as a bright yellow oil*; ν_{max}/cm^{-1} (film) 2083, 1654, 1585, 1546, 1353; δ_H (400 MHz, $CDCl_3$) 2.10 [3H, br s, $CN_2C(1)\underline{H}_3$], 4.60 [2H, d, *J* 6.0, $NC\underline{H}_2CHCH_2$], 5.19 [1H, finely split dd, *J* 17.2, 0.8, one of $NCH_2CHC\underline{H}_2$], 5.29 [1H, d with further unresolved splitting, *J* 10.4, one of $NCH_2CHC\underline{H}_2$], 5.89–6.00 [1H, m, $NCH_2C\underline{H}CH_2$], 6.28 [1H, dd, *J* 6.8, 6.8, C(5')H], 7.43 [1H, dd, *J* 6.8, 2.0, C(4')H], 7.75 [1H, br d with further unresolved splitting, *J* 5.6, C(6')H].

* Residual *p*-NBSA **166** present in sample.

1-Bromo-3-diazopropan-2-one 147[143]

Method A: Diazomethane acylation[143]

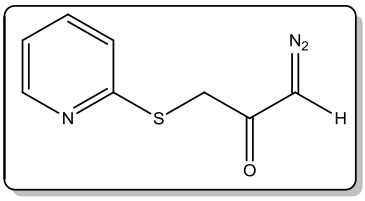


A solution of bromoacetyl bromide (0.2 mL, 1.92 mmol) in ether (10 mL) was added dropwise over 30 min to an ethereal solution of diazomethane **15** [prepared from Diazald® (3.50 g, 16.3 mmol)] while stirring at –20 °C. The reaction mixture was then allowed to slowly return to room temperature over 5 h. The ether and residual diazomethane were evaporated under reduced pressure at *ca.* 15 °C, using a rotary evaporator fitted with an acetic acid trap. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-bromo-α'-diazoketone* **147** (0.43 g, quantitative yield) ν_{max}/cm^{-1} (film) 2111, 1636 br, 1364 br; δ_H (400 MHz, $CDCl_3$) 3.85 [2H, br s, $C(3)\underline{H}_2$], 5.83 [1H, br s, $C(1)\underline{H}N_2$]. Spectral properties were consistent with previously reported data.[143]

Method B: Trimethylsilyldiazomethane acylation[298]

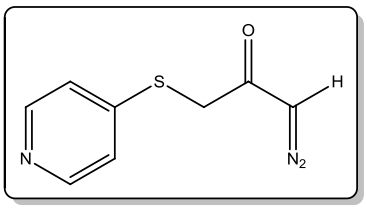
Bromoacetyl bromide (0.3 mL, 3.96 mmol) was dissolved in tetrahydrofuran/acetonitrile (20/20 mL) and added dropwise to a solution of trimethylsilyldiazomethane **131** (2.0 M in hexanes, 4.0 mL, 7.92 mmol) in tetrahydrofuran/acetonitrile (20/20 mL) at 0 °C. The glassware was covered with tinfoil to prevent degradation of the trimethylsilyldiazomethane **131** in the presence of sunlight. The reaction mixture was stirred for 4 h at 0 °C. The solvent and residual diazomethane **15** was removed under reduced pressure, using a rotary evaporator fitted with an acetic acid in solvent collection bulbs to afford the crude *bromodiazoketone*. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) provided the pure *α-bromo-α'-diazoketone* **147** (0.32 g, 49%) as a viscous yellow oil. Spectral properties were consistent with those obtained using method A.

1-Diazo-3-(pyridin-2-ylthio)propan-2-one 146[143]



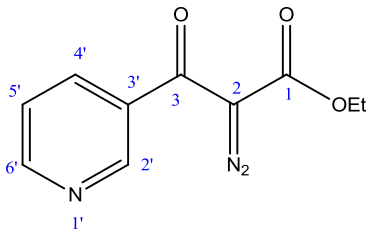
A suspension containing sodium methoxide (0.14 g, 2.60 mmol) and 2-mercaptopyridine **148** (0.29 g, 2.60 mmol) in tetrahydrofuran (15 mL) was added dropwise to a tetrahydrofuran solution (7 mL) of α-bromo-α'-diazoketone **147** (0.43 g, 2.60 mmol) while stirring at room temperature. The pressure equalised addition funnel was subsequently rinsed with additional tetrahydrofuran (~10 mL). The reaction mixture was heated under reflux for 1 h, followed by gravity filtration and removal of solvent under reduced pressure to yield the crude *diazoketone* as an orange/brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) and then flushed with methanol gave the pure *α-diazoketone* **146** (0.21 g, 42%) as a bright yellow oil which solidified upon storage at 5 °C overnight; ν_{max}/cm^{-1} (film) 3056, 2106, 1633 br, 1579, 1557, 1455, 1416, 1350 br, 1123, 1072, 759; δ_H (400 MHz, $CDCl_3$) 3.93 [2H, br s, C(3)$\underline{H}_2$], 5.78 [1H, br s, C(1)$\underline{H}N_2$], 7.01 [1H, t with further unresolved splitting, *J* 6.0, C(5')$\underline{H}$], 7.20 [1H, d with further unresolved splitting, *J* 8.0, C(3')$\underline{H}$], 7.47–7.56 [1H, m, C(4')$\underline{H}$], 8.42 [1H, d with further unresolved splitting, *J* 4.8, C(6')$\underline{H}$]. Spectral properties were consistent with previously reported data.[143]

1-Diazo-3-(pyridin-4-ylthio)propan-2-one 150



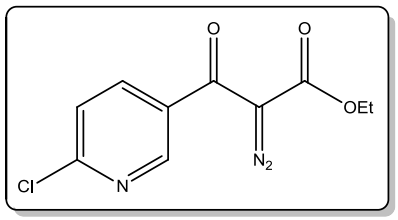
This was prepared following the procedure described for **146**, from a solution of α-bromo-α'-diazoketone **147** (0.26 g, 1.61 mmol) in tetrahydrofuran (7 mL), a suspension of sodium methoxide (0.09 g, 1.61 mmol) and 4-mercaptopyridine **149** (0.18 g, 1.61 mmol) in tetrahydrofuran (15 mL) to provide the crude *diazoketone* as orange/brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (80:20) and then flushed with methanol gave the pure *α-diazoketone* **150** (0.13 g, 41%) as a dark yellow oil; ν_{max}/cm^{-1} (film) 3098, 2109, 1630, 1578, 1541, 1484, 1411, 1360, 1131, 804, 708; δ_H (300 MHz, $CDCl_3$) 3.72 [2H, br s, C(3)$\underline{H}_2$], 5.80 [1H, br s, C(1)$\underline{H}N_2$], 7.14 [2H, d, *J* 6.3, C(3')$\underline{H}$ and C(5')$\underline{H}$], 8.43 [2H, d, *J* 6.3, C(2')$\underline{H}$ and C(6')$\underline{H}$]; δ_C (75.5 MHz, DMSO-d_6) 37.40 [CH_2, $\underline{C}$(3)H_2], 55.0 [CH, br, $\underline{C}$(1)HN_2], 120.5 [2 × CH, $\underline{C}$(3')H and $\underline{C}$(5')H], 147.4 [C, $\underline{C}$(4')], 149.2 [2 × CH, $\underline{C}$(2')H and $\underline{C}$(6')H], 189.5 [C, $\underline{C}$(2)=O]; HRMS (ES+): Exact mass calculated for $C_8H_8NO_3S$ $[M+H]^+$, 194.0388. Found 194.0384. m/z (ES+) 194.0 $[(M+H)^+$, 100%].

Synthesis of α-diazo-β-ketoesters



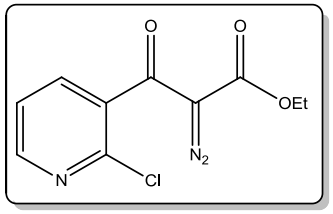
General numbering scheme for α-diazo-β-ketoesters

Ethyl-3-(6-chloropyridin-3-yl)-2-diazo-3-oxopropanoate 157



This procedure is based on a method described by Miyamoto for the preparation of **159**.[64] 6-Chloronicotinoyl chloride **60** (1.00 g, 5.68 mmol) and ethyl diazoacetate (1.8 mL, 17.00 mmol) were placed in a round-bottom flask and the reaction mixture warmed to 55 °C and stirred for 3 h; then stirred at ambient temperature for 18 h. The reaction mixture was concentrated under reduced pressure to afford the crude *α-diazo-β-ketoester* as a bright yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *α-diazo-β-ketoester* **157** (0.99 g, 69%) as a yellow oil which later solidified; m.p. 38–41 °C; ν_{max}/cm^{-1} (film) 2984, 2150, 1721, 1628, 1583, 1458, 1371, 1317, 1269, 1176, 1125, 1103, 929, 758; δ_H (300 MHz, $CDCl_3$) 1.23 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.21 [2H, q, *J* 6.9, $C\underline{H}_2CH_3$], 7.34 [1H, dd, *J* 8.4, 0.6, C(5')H], 7.85 [1H, dd, *J* 8.4, 2.4, C(4')H], 8.57 [1H, dd, *J* 2.4, 0.6, C(2')H]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH_3, $CH_2\underline{C}H_3$], 60.3 [C, C(2)N_2], 61.9 [CH_2, $\underline{C}H_2CH_3$], 123.4 [CH, C(5')H], 131.5 [C, C(3')], 138.5 [CH, C(4')H], 149.5 [CH, C(2')H], 154.5 [C, C(6')Cl], 160.3 [C, C(1)=O], 183.9 [C, C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_9{}^{35}ClN_3O_3$ $[M+H]^+$, 254.0325. Found 254.0322. Exact mass calculated for $C_{10}H_9{}^{37}ClNO_3$ $[(M+H)–N_2]^+$, 228.0241. Found 228.0248 and exact mass calculated for $C_{10}H_9{}^{35}ClNO_3$ $[(M+H)–N_2]^+$, 226.0271. Found 226.0269. m/z (ES+) 256.1 {$[(C_{10}H_9{}^{37}ClN_3O_3)^+]$, 34%}, 254.0 {$[(C_{10}H_9{}^{35}ClN_3O_3)^+]$, 100%}, 129.1 (12%), 87.9 (41%).

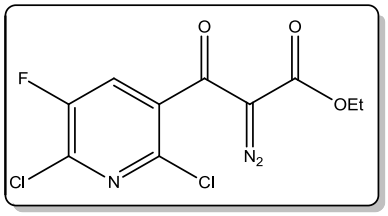
Ethyl-3-(2-chloropyridin-3-yl)-2-diazo-3-oxopropanoate 158[145]



This was prepared following the procedure described for **157**, from 2-chloronicotinoyl chloride **56** (1.47 g, 8.34 mmol) and ethyl diazoacetate (2.9 mL, 25.03 mmol) to afford the crude *α-diazo-β-ketoester* as a bright yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to furnish the pure *α-diazo-β-ketoester* **158** (1.17 g, 55%)* as a yellow oil which later solidified; m.p. 36–38 °C; ν_{max}/cm^{-1} (film) 2985, 2152, 1723, 1636, 1579, 1562, 1400, 1372, 1327, 1306, 1181, 1128, 1078, 933, 756; δ_H (300 MHz, $CDCl_3$) 1.17 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.18 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.34 [1H, dd, *J* 7.5, 4.8, C(5')H], 7.64 [1H, dd, *J* 7.5, 1.8, C(4')H], 8.48 [1H, dd, *J* 4.8, 1.8, C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 13.9 [CH_3, $CH_2\underline{C}H_3$], 61.9 [CH_2, $\underline{C}H_2CH_3$], 62.8 [C, C(2)N_2], 122.1 [CH, C(5')H], 134.3 [C, C(3')], 136.6 [CH, C(4')H], 147.0 [C, C(2')Cl], 150.5 [CH, C(2')H], 160.0 [C, C(1)=O], 184.1 [C, C(3)=O]. Spectral properties were consistent with previously reported data.[145]

* Sample contains residual ethyl acetate.

Ethyl-2-diazo-3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate 159[64]

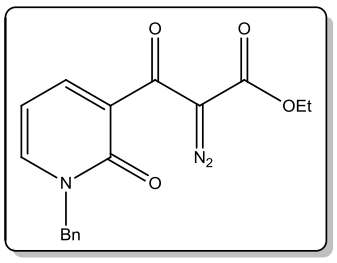


This was prepared following the procedure described for **157**, from 2,6-dichloro-5-fluoronicotinoyl chloride **59** (2.31 g, 10.10 mmol) and ethyl diazoacetate (3.2 mL, 30.30 mmol) to give the crude *α-diazo-β-ketoester* as a bright yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) provided the *α-diazo-β-ketoester* **159** (0.37 g, 11%) as a yellow oil which later solidified which by ^{1}H NMR is ~60% pure; m.p. 75–78 °C (lit.,[64] 89–90 °C); ν_{max}/cm^{-1} (film) 2985, 2148, 2114, 1723, 1639, 1398, 1322, 1260, 1120; δ_H (300 MHz, $CDCl_3$)* 1.24 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.23 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 7.46 [1H, d, J_{HF} 6.9, C(4')H]. Spectral properties were consistent with previously reported data.[64]

* Sample contains residual ethyl acetate and a significant amount of co-eluting ethyl diazoacetate. The infrared signals for ethyl diazoacetate are ν_{max}/cm^{-1} (film) 2984, 2114, 1784, 1742, 1696, 1579, 1368, 1209, 1107. The ^{1}H NMR signals are δ_H (300 MHz, $CDCl_3$) 1.28 [3H, t, *J* 9.0, $CH_2C\underline{H}_3$], 4.22 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 4.75 [1H, br s, $C\underline{H}N_2$].

Single crystals of ethyl-2-diazo-3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate **159** were grown from deuterated chloroform. Crystal data: $C_{10}H_6Cl_2FN_3O_3$, M = 306.08, monoclinic, $P2_1/c$, a = 7.627(6) Å, b = 20.599(18) Å, c = 8.161(7) Å, β = 93.33(3)°, V = 1280.0(18) Å^3, Z = 4, D_c = 1.588 g cm^{-3}, F_{000} = 616, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.11°, μ = 0.526 mm^{-1}, 8908 reflections collected, 2250 unique (R_{int} = 0.1113), final GooF = 0.885, R_1 = 0.0631, wR_2 = 0.1683 (1079 obs. data: $I > 2\sigma(I)$); R_1 = 0.1492, wR_2 = 0.2507 (all data). Full details are given in *Appendix III*.

Ethyl 3-(1-benzyl-2-oxo-1,2-dihydropyridin-3-yl)-2-diazo-3-oxopropanoate 161

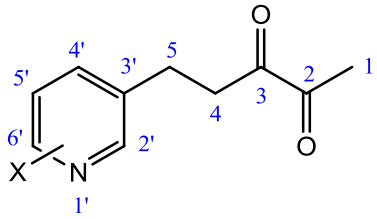


This was prepared following the procedure described for **157**, from the crude acid chloride **160** (2.50 g, 10.09 mmol) and ethyl diazoacetate (3.2 mL, 30.28 mmol) to furnish the crude α-*diazo-β-ketoester* as a brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *α-diazo-β-ketoester* **160** (0.73 g, 23%) as a brown oil; ν_{max}/cm^{-1} (film) 2983, 2133, 1723, 1655, 1594, 1547, 1314; δ_H (300 MHz, $CDCl_3$) 1.21 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.21 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 5.13 [2H, s, $NC\underline{H}_2C_6H_5$], 6.22 [1H, dd, *J* 6.9, 6.6, C(5')H], 7.25–7.37 [5H, m, 5 × aromatic H], 7.42 [1H, dd, *J* 6.9, 2.1, C(4')H or C(6')H], 7.54 [1H, dd, *J* 6.9, 2.1, C(4')H or C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 14.1 [CH_3, $CH_2\underline{C}H_3$], 52.2 [CH_2, $N\underline{C}H_2C_6H_5$], 60.3 [C, $\underline{C}(2)N_2$], 61.4 [CH_2, $\underline{C}H_2CH_3$], 105.6 [CH, $\underline{C}$(5')H], 128.15 [CH, aromatic $\underline{C}$H], 128.23 [CH, 2 × aromatic $\underline{C}$H], 128.9 [CH, 2 × aromatic $\underline{C}$H], 130.7 [C, $\underline{C}$(3')], 135.8 [C, aromatic $\underline{C}$], 139.8 [CH, $\underline{C}$(4')H or $\underline{C}$(6')H], 140.3 [CH, $\underline{C}$(4')H or $\underline{C}$(6')H], 159.6 [C, $\underline{C}$(1)=O or $\underline{C}$(2')=O], 160.9 [C, $\underline{C}$(1)=O or $\underline{C}$(2')=O] 184.5 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated for $C_{17}H_{16}NO_4$ $[(M+H)–N_2]^+$, 298.1063. Found 298.1073. m/z (ES+) 300.2 (4%), 299.1 (6%), 298.1 {$[(C_{17}H_{16}N_3O_4–N_2)^+]$, 100%}.

Transition metal-catalysed transformations of α-diazoketones and α-diazo-β-ketoesters

(i) Formation of 2,3-diketones from rhodium(II)-mediated α-diazoketone transformations and subsequent synthesis of diazanaphthalenes (quinoxalines)

Preparation of 2,3-diketones

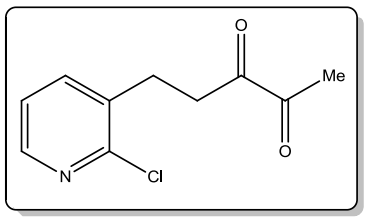


General numbering Scheme for 2,3-diketones

Initial 2,3-diketones **209**, **210**, **212** and **213** were isolated unexpectedly from reactions of α-diazoketones with $Rh_2(OAc)_4$ as described below. Having identified the 2,3-diketones as the principal products from the rhodium(II)-mediated reaction of the α-diazoketones, subsequent synthesis of 2,3-diketones was effected by exposure of **63-65**, **136**, **137**, **139** to $Rh_2(OAc)_4$ in singly distilled dichloromethane under air *cf.* nitrogen. In these cases, the 2,3-diketones were not isolated but were carried through crude to the formation of quinoxalines following initial check by ^{1}H NMR and infrared spectroscopy.

In these reactions, no colour change was observed upon addition of the $Rh_2(OAc)_4$ catalyst to the yellow reaction mixture of α-diazoketone and singly/doubly distilled dichloromethane. In cases where two portions of the rhodium catalyst were added (*i.e.* 2 × 1 mol%), the second portion was introduced following addition of half of the α-diazoketone solution to the catalyst/solvent mixture.

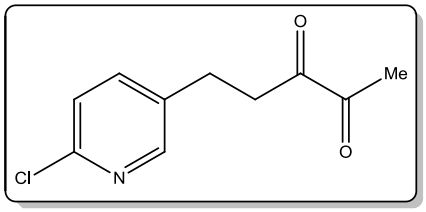
5-(2-Chloropyridin-3-yl)pentane-2,3-dione 209



A solution of 5-(2-chloropyridin-3-yl)-2-diazopentan-3-one **134** (0.08 g, 0.36 mmol) in doubly distilled dichloromethane (30 mL) was added dropwise over ~1 h to a stirring solution of $Rh_2(OAc)_4$ (2 × 1.78 mg, 2 × 1 mol%) in doubly distilled dichloromethane (40 mL) and the reaction mixture was stirred at room temperature under nitrogen. The reaction mixture was stirred for a further 1 h at room temperature and the reaction progress was monitored by TLC analysis and infrared analysis. Removal of solvent under reduced pressure provided the crude *2,3-diketone* as a pale brown oil which is ~80–90% pure by ^{1}H NMR. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *2,3-diketone* **209** (0.03 g, 37%) as a yellow oil; ν_{max}/cm^{-1} (film) 2933, 1716, 1566, 1412, 1355, 1071; δ_H (400 MHz, $CDCl_3$) 2.35 [3H, s, C(1)$\underline{H}_3$], 3.02 [2H, t, *J* 7.2, C(4)$\underline{H}_2$], 3.17 [2H, t, *J* 7.2, C(5)$\underline{H}_2$], 7.19 [1H, dd, *J* 7.6, 4.8, C(5')$\underline{H}$], 7.62 [1H, dd, *J* 7.6, 2.0, C(4')$\underline{H}$], 8.27 [1H, dd, *J* 4.8, 2.0, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 23.6 [CH_3, $\underline{C}(1)H_3$], 26.5 [CH_2, $\underline{C}(5)H_2$], 34.9

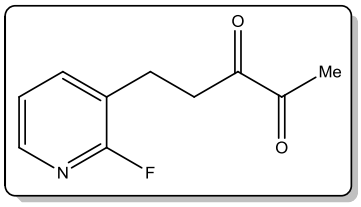
[CH_2, C(4)H_2], 122.6 [CH, C(5')H], 134.5 [C, C(3')], 139.3 [CH, C(4')H], 147.8 [CH, C(6')H], 151.2 [C, C(2')Cl], 196.8 and 197.4 [2 × C, C(2)=O and C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{37}ClNO_2$ $[M+H]^+$, 214.0448. Found 214.0464 and exact mass calculated for $C_{10}H_{11}{}^{35}ClNO_2$ $[M+H]^+$, 212.0478. Found 212.0484. m/z (ES+) 214.0 {[$(C_{10}H_{11}{}^{37}ClNO_2)^+$], 35%}, 212.0 {[$(C_{10}H_{11}{}^{35}ClNO_2)^+$], 100%}.

5-(6-Chloropyridin-3-yl)pentane-2,3-dione 210



The title compound was prepared following the procedure described for **209**, from a solution of 5-(6-chloropyridin-3-yl)-2-diazopentan-3-one **135** (0.09 g, 0.42 mmol) in doubly distilled dichloromethane (30 mL) and $Rh_2(OAc)_4$ (2 × 1.78 mg, 2 × 1 mol%) dissolved in doubly distilled dichloromethane (40 mL) to provide the crude *diketone* as a pale brown oil which is ~80–90% pure by ^{1}H NMR. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) to (40:60) gave the pure *2,3-diketone* **210** (0.03 g, 29%) as a yellow oil; ν_{max}/cm^{-1} (film) 2929, 1714, 1566, 1461, 1353, 1107, 1067; δ_H (400 MHz, $CDCl_3$) 2.33 [3H, s, C(1)H_3], 2.90 [2H, t, *J* 7.6, C(4)H_2], 3.09 [2H, t, *J* 7.6, C(5)H_2], 7.25 [1H, d, *J* 8.4, C(5')H], 7.51 [1H, dd, *J* 8.4, 2.4, C(4')H], 8.25 [1H, d, *J* 2.4, C(2')H]; δ_C (75.5 MHz, $CDCl_3$) 23.6 [CH_3, C(1)H_3], 25.3 [CH_2, C(5)H_2], 36.7 [CH_2, C(4)H_2], 124.0 [CH, C(5')H], 134.7 [C, C(3')], 138.9 [CH, C(4')H], 149.5 [C, C(6')Cl], 149.6 [CH, C(2')H], 196.8 and 197.2 [2 × C, C(2)=O and C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{37}ClNO_2$ $[M+H]^+$, 214.0448. Found 214.0455 and exact mass calculated for $C_{10}H_{11}{}^{35}ClNO_2$ $[M+H]^+$, 212.0478. Found 212.0478. m/z (ES+) 214.0 {[$(C_{10}H_{11}{}^{37}ClNO_2)^+$], 36%}, 212.0 {[$(C_{10}H_{11}{}^{35}ClNO_2)^+$], 100%}.

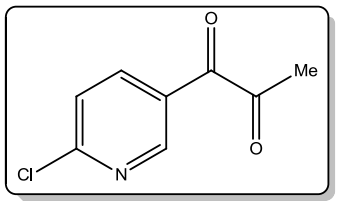
5-(2-Fluoropyridin-3-yl)pentane-2,3-dione 212



The title compound was prepared following the procedure described for **209**, from a solution of 2-diazo-5-(2-fluoropyridin-3-yl)pentan-3-one **138** (0.09 g, 0.45 mmol) in doubly distilled dichloromethane (40 mL) and $Rh_2(OAc)_4$ (4.4 mg, 2 mol%) dissolved in doubly distilled dichloromethane (40 mL) to afford the crude *diketone* as a pale brown oil which is ~80–90% pure by ^{1}H NMR. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *2,3-diketone* **212** (0.01 g, 15%) as a yellow oil; ν_{max}/cm^{-1} (film) 2927, 1735, 1716, 1608, 1579, 1439, 1245; δ_H (300 MHz, $CDCl_3$) 2.35 [3H, s, C(1)H_3]*, 2.94 [2H, t, *J* 6.9, C(4)H_2]*, 3.15 [2H, t, *J* 7.2, C(5)H_2]*, 7.12 [1H, ddd, *J* 7.2, 4.8, 1.8, C(5')H], 7.66 [1H, ddd, *J* 9.6, 7.5, 2.1, C(4')H], 8.08 [1H, br d with further unresolved splitting, *J* 4.5, C(6')H].

* Integration is lower than expected.

3-(6-Chloropyridin-3-yl)propane-2,3-dione 213

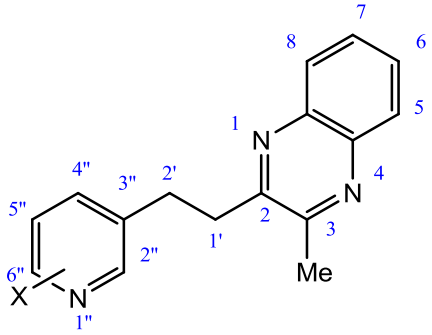


The title compound was prepared following the procedure described for **209**, from a solution of 3-(6-chloropyridin-3-yl)-2-diazopropan-3-one **63** (0.20 g, 1.03 mmol) in doubly distilled dichloromethane (30 mL) and $Rh_2(OAc)_4$ (2 × 1.78 mg, 2 × 1

mol%) dissolved in doubly distilled dichloromethane (40 mL) to afford the crude *diketone* as a pale brown oil which is ~50% pure by ^{1}H NMR. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *2,3-diketone* **213** (0.01 g, 6%) as a yellow oil; ν_{max}/cm^{-1} (film) 1721, 1675; δ_H (400 MHz, $CDCl_3$) 2.55 [3H, s, C(1)$\underline{H}_3$], 7.47 [1H, dd, *J* 8.4, 0.6, C(5')$\underline{H}$], 8.33 [1H, dd, *J* 8.4, 2.4, C(4')$\underline{H}$], 9.07 [1H, d, *J* 2.4, C(6')$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 25.7 [CH_3, $\underline{C}(1)H_3$], 124.6 [CH, $\underline{C}(5')H$], 126.8 [C, $\underline{C}(3')$], 140.1 [CH, $\underline{C}(4')H$], 152.2 [CH, $\underline{C}(2')H$], 156.8 [C, $\underline{C}(6')Cl$], 187.3* [C, $\underline{C}(2)$=O or $\underline{C}(3)$=O], 198.2* [C, $\underline{C}(2)$=O or $\underline{C}(3)$=O].

* The chemical shifts are in good agreement with those described for phenyl analogue **214** prepared by Stergiou and co-workers,[212] although definitive assignment of $\underline{C}(2)$=O and $\underline{C}(3)$=O was not disclosed in that work.

Preparation of diazanaphthalenes (quinoxalines)



Numbering scheme for diazanaphthalenes

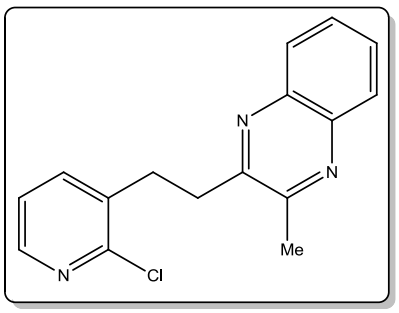
The quinoxalines were prepared *via* two methods in this work;

a) Isolation of the 2,3-diketones by chromatography and condensation with 1,2-diaminobenzene **215**, and

b) Generation of 2,3-diketones without purification and subsequent condensation with 1,2-diaminobenzene **215**.

Quinoxalines synthesised *via* Method A: Isolation of the 2,3-diketones by chromatography and condensation with 215

2-[2-(2-Chloropyridin-3-yl)ethyl]-3-methylquinoxaline 227



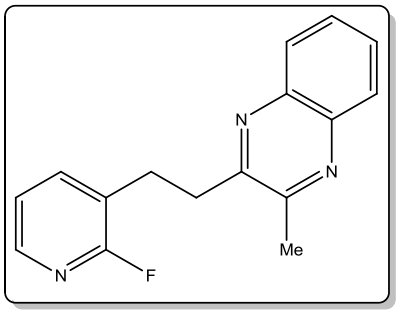
1,2-Diaminobenzene **215*** (0.04 g, 0.39 mmol) was added in one portion to a stirring solution of 2,3-diketone **209** (0.05 g, 0.19 mmol) in singly distilled dichloromethane (40 mL) at room temperature. The reaction mixture was stirred for 1 h at room temperature with the reaction progress monitored by TLC analysis. The reaction mixture was then concentrated *in vacuo* to give the crude *quinoxaline* as a brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *quinoxaline* **227** (0.03 g, 54%) as a yellow oil which subsequently solidified; m.p. 136–138 °C; ν_{max}/cm^{-1} (film) 2922, 1686, 1654, 1638, 1561, 1406, 1120, 1072, 794, 770, 751; δ_H (300 MHz, $CDCl_3$)

2.74 [3H, s, C(3)C$\underline{H}_3$], 3.31–3.39 [4H, m, C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$], 7.17 [1H, dd, *J* 7.5, 4.8, C(5")$\underline{H}$], 7.63–7.73 [3H, m, C(4")$\underline{H}$, C(6)$\underline{H}$ and C(7)$\underline{H}$], 7.95–8.07 [2H, m, C(5)$\underline{H}$ and C(8)$\underline{H}$], 8.28 [1H, dd, *J* 4.8, 1.8, C(6")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 22.7 [CH_3, C(3)$\underline{C}H_3$], 31.1 [CH_2, $\underline{C}$(2')H_2], 34.6 [CH_2, $\underline{C}$(1')H_2], 122.7 [CH, $\underline{C}$(5")H], 128.3, 128.5, 128.9, 129.2 [4 × CH, $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 135.5 [C, $\underline{C}$(3")], 139.5 [CH, $\underline{C}$(4")H], 140.9 and 141.0 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 147.7 [CH, $\underline{C}$(6")H], 151.3 [C, $\underline{C}$(2")Cl], 153.1 and 154.6 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)]; HRMS (ES+): Exact mass calculated for $C_{16}H_{15}{}^{37}ClN_3$ $[M+H]^+$, 286.0925. Found 286.0923 and exact mass calculated for $C_{16}H_{15}{}^{35}ClN_3$ $[M+H]^+$, 284.0955. Found 284.0951. m/z (ES+) 286.0 {$[(C_{16}H_{15}{}^{37}ClN_3)^+]$, 34%}, 284.1 {$[(C_{16}H_{15}{}^{35}ClN_3)^+]$, 100%}.

Single crystals of 2-[2-(2-chloropyridin-3-yl)ethyl]-3-methylquinoxaline **227** were grown from deuterated chloroform. Crystal data: $C_{16}H_{14}ClN_3$, M = 283.75, monoclinic, $P2_1/c$, a = 8.3417(3) Å, b = 22.9470(10) Å, c = 7.2431(3) Å, β = 95.2440(10)°, V = 1380.65(10) Å^3, Z = 4, D_c = 1.365 g cm^{-3}, F_{000} = 592, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.98°, μ = 0.269 mm^{-1}, 15959 reflections collected, 2679 unique (R_{int} = 0.0307), final GooF = 2.002, R_1 = 0.0365, wR_2 = 0.0947 (2242 obs. data: $I > 2\sigma(I)$); R_1 = 0.0462 wR_2 = 0.0973 (all data). Full details are given in *Appendix III*.

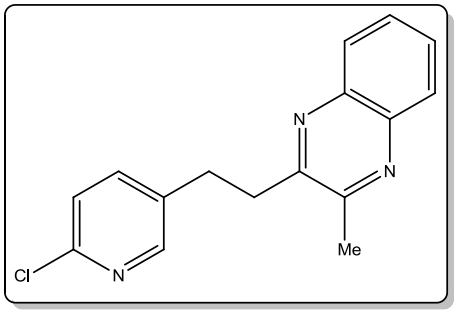
* 1,2-Diaminobenzene **215** (0.99 g, 9.20 mmol) was freshly purified by hot recrystallisation from dichloromethane followed by treatment with activated charcoal which was filtered to remove the coloured impurities.[11,231] This gave the purified amine **215** as a pale pink solid (0.44 g, 45% recovery) which was used for the condensation reaction with purified 2,3-diketone **209**. Previous reports within the research group had described the purification by recrystallisation from a saturated solution of sodium dithionate.[8]

2-[2-(2-Fluoropyridin-3-yl)ethyl]-3-methylquinoxaline 228



This was prepared following the procedure described for **227** (Method A: From purified 2,3-diketone), from 1,2-diaminobenzene **215** (0.02 g, 0.14 mmol) and a solution of 2,3-diketone **212** (0.01 g, 0.07 mmol) in singly distilled dichloromethane (40 mL) to furnish the crude *quinoxaline* as a brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *quinoxaline* **228** (0.02 g, quantitative yield) as a white solid; m.p. 118–119 °C; ν_{max}/cm^{-1} (KBr) 2920, 1654, 1636, 1612, 1582, 1491, 1444, 1400, 1236, 1188, 1102, 780; δ_H (300 MHz, $CDCl_3$) 2.74 [3H, s, C(3)C$\underline{H}_3$], 3.23–3.36 [4H, m, C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$], 7.11 [1H, ddd, *J* 7.2, 4.8, 1.8, C(5")$\underline{H}$], 7.66–7.77 [3H, m, C(4")$\underline{H}$, C(6)$\underline{H}$ and C(7)$\underline{H}$], 7.96–8.06 [2H, m, C(5)$\underline{H}$ and C(8)$\underline{H}$], 8.08 [1H, poorly resolved dt, *J* 4.8, 1.8, C(6")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 22.7 [CH_3, C(3)$\underline{C}H_3$], 26.8 [CH_2, d, $^3J_{CF}$ 2.2, $\underline{C}$(2')H_2], 34.9 [CH_2, $\underline{C}$(1')H_2], 121.5 [CH, d, $^4J_{CF}$ 4.2, $\underline{C}$(5")H], 123.1 [C, d, $^2J_{CF}$ 30.6, $\underline{C}$(3")], 128.3, 128.5, 128.9, 129.1 [4 × CH, $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 140.9 and 141.0 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 141.3 [CH, d, $^3J_{CF}$, 6.0, $\underline{C}$(4")H], 145.5 [CH, d, $^3J_{CF}$ 14.7, $\underline{C}$(6")H] 153.0 and 154.5 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)], 162.2 [C, d, $^1J_{CF}$ 238.4, $\underline{C}$(2")F]; HRMS (ES+): Exact mass calculated for $C_{16}H_{15}FN_3$ $[M+H]^+$, 268.1250. Found 268.1244. m/z (ES+) 269.1 (20%), 268.1 $[(M+H)^+$, 100%].

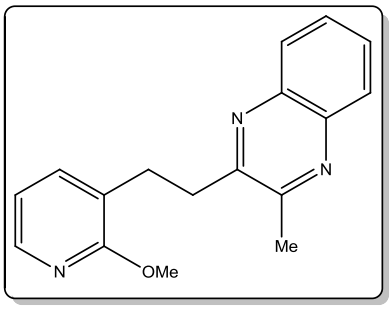
2-[2-(6-Chloropyridin-3-yl)ethyl]-3-methylquinoxaline 230



This was prepared following the procedure described for **227** (Method A: From purified 2,3-diketone), from 1,2-diaminobenzene **215** (0.03 g, 0.26 mmol) and a solution of 2,3-diketone **210** (0.03 g, 0.12 mmol) in singly distilled dichloromethane (40 mL) to afford the crude *quinoxaline* as a brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *quinoxaline* **230** (0.02 g, 56%) as a yellow oil which subsequently solidified; m.p. 118–120 °C; ν_{max}/cm^{-1} (film) 1650, 1563, 1456, 1388, 1316, 1203, 1104, 759; δ_H (300 MHz, $CDCl_3$) 2.71 [3H, s, C(3)C$\underline{H}_3$], 3.22–3.32 [4H, m, C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$], 7.24 [1H, d, *J* 8.4, C(5")$\underline{H}$], 7.58 [1H, dd, *J* 8.4, 2.4, C(4")$\underline{H}$], 7.65–7.72 [2H, m, C(6)$\underline{H}$ and C(7)$\underline{H}$], 7.96–8.03 [2H, m, C(5)$\underline{H}$ and C(8)$\underline{H}$], 8.36 [1H, d, *J* 2.4, C(2")$\underline{H}$]; δ_C (125.8 MHz, $CDCl_3$) 22.7 [CH_3, C(3)$\underline{C}H_3$], 29.4 [CH_2, $\underline{C}$(2')H_2], 36.4 [CH_2, $\underline{C}$(1')H_2], 124.0 [CH, $\underline{C}$(5")H], 128.4, 128.6, 129.0, 129.2 [4 × CH, $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 135.8 [C, $\underline{C}$(3")], 139.0 [CH, $\underline{C}$(4")H], 140.99 and 141.01 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 149.3 [C, $\underline{C}$(6")Cl], 149.9 [CH, $\underline{C}$(2")H], 152.8 and 154.2 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)]; HRMS (ES+): Exact mass calculated for $C_{16}H_{15}{}^{37}ClN_3$ $[M+H]^+$, 286.0925. Found 286.0923 and exact mass calculated for $C_{16}H_{15}{}^{35}ClN_3$ $[M+H]^+$, 284.0955. Found 284.0944. m/z (ES+) 286.0 {$[(C_{16}H_{15}{}^{37}ClN_3)^+]$, 35%}, 284.0 {$[(C_{16}H_{15}{}^{35}ClN_3)^+]$, 100%}.

Quinoxalines prepared *via* Method B: Generation of 2,3-diketones without purification and condensation with 215

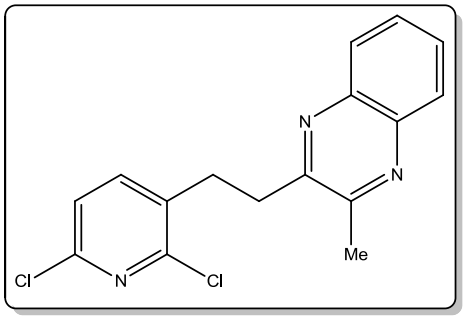
2-[2-(2-Methoxypyridin-3-yl)ethyl]-3-methylquinoxaline 229



A solution of α-diazoketone **139** (0.06 g, 0.27 mmol) in singly distilled dichloromethane (40 mL) was treated with $Rh_2(OAc)_4$ (1.35 mg, 1 mol%) and the solution was stirred for 1 h at room temperature, under air. There was no change in colour observed in the reaction mixture on addition of the catalyst. Reaction progress was monitored by TLC analysis and infrared spectroscopy and was complete after 1 h. Concentration under reduced pressure afforded the crude *2,3-diketone* as a yellow oil which was confirmed by ^{1}H NMR and infrared spectroscopic analysis (~80–90% pure by ^{1}H NMR); ν_{max}/cm^{-1} (film) 2925, 1714, 1594, 1467, 1444, 1413; δ_H (400 MHz, $CDCl_3$) 2.33 [3H, s, C(1)$\underline{H}_3$], 2.86 [2H, t, *J* 7.6, C(4)$\underline{H}_2$], 3.06 [2H, t, *J* 7.6, C(5)$\underline{H}_2$], 3.94 [3H, s, OC$\underline{H}_3$], 6.80 [1H, dd, *J* 7.2, 5.2, C(5')$\underline{H}$], 7.41 [1H, dd, *J* 7.2, 2.0, C(4')$\underline{H}$], 8.03 [1H, dd, *J* 5.2, 2.0, C(6')$\underline{H}$]. The crude *2,3-diketone* was dissolved in singly distilled dichloromethane (40 mL) and stirred at room temperature. 1,2-Diaminobenzene **215** (0.05 g, 0.46 mmol) was added in one portion and the reaction mixture was stirred for 1 h at room temperature with reaction progress monitored by TLC analysis. Evaporation of solvent under reduced pressure provided the crude *quinoxaline* as a yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *quinoxaline* **229** (0.04 g, 50% from α-diazoketone) as a yellow crystalline solid. m.p. 71–72 °C; ν_{max}/cm^{-1} (KBr) 2949, 1738, 1587, 1466, 1452, 1412, 1313,

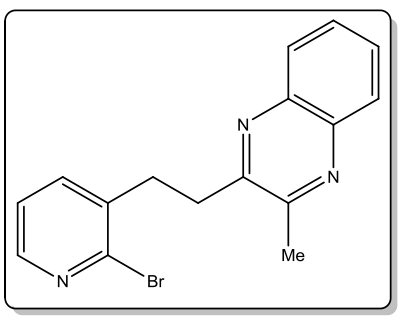
1257, 1105, 1022, 761; δ_H (300 MHz, $CDCl_3$) 2.73 [3H, s, C(3)C$\underline{H}_3$], 3.08–3.16 and 3.22–3.33 [2 × 2H, 2 × m, C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$], 3.94 [3H, s, OC$\underline{H}_3$], 6.80 [1H, dd, *J* 6.9, 4.8, C(5")$\underline{H}$], 7.45 [1H, dd, *J* 7.2, 1.8, C(4")$\underline{H}$], 7.62–7.71 [2H, m, C(6)$\underline{H}$ and C(7)$\underline{H}$], 7.94–8.06 [3H, m, C(5)$\underline{H}$, C(8)$\underline{H}$ and C(6")$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 22.6 [CH_3, C(3)$\underline{C}H_3$], 28.7 [CH_2, $\underline{C}$(2')H_2], 35.1 [CH_2, $\underline{C}$(1')H_2], 53.2 [CH_3, O$\underline{C}H_3$], 116.8 [CH, $\underline{C}$(5")H], 123.7 [C, $\underline{C}$(3")], 128.3, 128.5, 128.8, 128.9 [4 × CH, $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 138.2 [CH, $\underline{C}$(4")H], 140.9 and 141.1 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 144.7 [CH, $\underline{C}$(6")H], 153.3 and 155.8 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)], 162.2 [C, $\underline{C}$(2")OCH_3]; HRMS (ES+): Exact mass calculated for $C_{17}H_{18}N_3O$ $[M+H]^+$, 280.1450. Found 280.1464. m/z (ES+) 280.3 $[(M+H)^+$, 100%].

2-[2-(2,6-Dichloropyridin-3-yl)ethyl]-3-methylquinoxaline 231



This was prepared following the procedure described for **229** (Method B: From non-purified 2,3-diketone) using diazoketone **136** (0.07 g, 0.26 mmol), singly distilled dichloromethane (40 mL) and $Rh_2(OAc)_4$ (2.64 mg, 1 mol%) to afford the crude *2,3-diketone* as a yellow oil (~80–90% pure by ^{1}H NMR); ν_{max}/cm^{-1} (film) 2922, 1715, 1580, 1552, 1427, 1143; δ_H (400 MHz, $CDCl_3$) 2.35 [3H, s, C(1)$\underline{H}_3$], 3.00 [2H, t, *J* 7.2, C(4)$\underline{H}_2$], 3.14 [2H, t, *J* 72, C(5)$\underline{H}_2$], 7.22 [1H, d, *J* 8.0, C(5')$\underline{H}$], 7.60 [1H, d, *J* 8.0, C(4')$\underline{H}$]. 1,2-Diaminobenzene **215** (0.07 g, 0.57 mmol) was added in one portion to a stirring solution of crude *2,3-diketone* in singly distilled dichloromethane (40 mL) to provide the crude *quinoxaline* as a yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) gave the pure *quinoxaline* **231** (0.03 g, 63%) as a yellow/brown solid; m.p. 103–105 °C; ν_{max}/cm^{-1} (KBr) 2919, 1654, 1637, 1620, 1578, 1560, 1542, 1424, 1140, 1070, 764, 669; δ_H (400 MHz, $CDCl_3$) 2.73 [3H, s, C(3)C$\underline{H}_3$], 3.26–3.39 [4H, m, C(1')$\underline{H}_2$ and C(2')$\underline{H}_2$], 7.19 [1H, d, *J* 7.8, C(5")$\underline{H}$], 7.63–7.73 [3H, m, C(4")$\underline{H}$, C(6)$\underline{H}$ and C(7)$\underline{H}$], 7.96–8.03 [2H, m, C(5)$\underline{H}$ and C(8)$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 22.7 [CH_3, C(3)$\underline{C}H_3$], 30.0 [CH_2, $\underline{C}$(2')H_2], 34.3 [CH_2, $\underline{C}$(1')H_2], 123.1 [CH, $\underline{C}$(5")H], 128.4, 128.5, 129.0, 129.2 [4 × CH, $\underline{C}$(5)H, $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 134.3 [C, $\underline{C}$(3")], 140.95 and 140.98 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 141.7 [CH, $\underline{C}$(4")H], 148.1 [C, $\underline{C}$(2")Cl or $\underline{C}$(6")Cl], 150.1 [C, $\underline{C}$(2")Cl or $\underline{C}$(6")Cl], 153.0 and 154.1 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)]; HRMS (ES+): Exact mass calculated for $C_{16}H_{14}{}^{35}Cl_2N_3$ $[M+H]^+$, 318.0565. Found 318.0578. m/z (ES+) 322.0 {$[(C_{16}H_{14}{}^{37}Cl_2N_3)^+]$, 20%}, 320.2 {$[(C_{16}H_{14}{}^{35}Cl^{37}ClN_3)^+]$, 68%}, 318.1 {$[(C_{16}H_{14}{}^{35}Cl_2N_3)^+]$, 100%}.

2-[2-(2-Bromopyridin-3-yl)ethyl]-3-methylquinoxaline 232



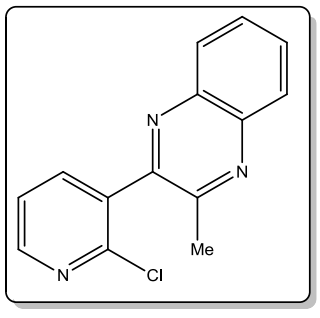
This was prepared following the procedure described for **229** (Method B: From non-purified 2,3-diketone), using diazoketone **137** (0.13 g, 4.92 mmol), singly distilled dichloromethane (40 mL) and $Rh_2(OAc)_4$ (4.92 mg, 1 mol%) to generate the crude *2,3-diketone* as a yellow oil (~80% pure by ^{1}H NMR); ν_{max}/cm^{-1} (film) 2935, 1714, 1560, 1405, 1052; δ_H (400 MHz, $CDCl_3$) 2.36 [3H, s, C(1)$\underline{H}_3$], 3.02 [2H, t, *J*

7.2, C(4)H$_2$], 3.16 [2H, t, *J* 7.2, C(5)H$_2$], 7.22 [1H, dd, *J* 7.6, 4.8, C(5')H], 7.59 [1H, dd, *J* 7.2, 1.6, C(4')H], 8.25 [1H, dd, *J* 4.8, 2.0, C(6')H]. 1,2-Diaminobenzene **215** (0.12 g, 1.13 mmol) was added in one portion to a stirring solution of crude *2,3-diketone* in singly distilled dichloromethane (40 mL) to provide the crude *quinoxaline* as an orange/brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) furnished the pure *quinoxaline* **232** (0.07 g, 43%) as an orange solid; m.p. 115–117 °C; ν_{max}/cm^{-1} (KBr) 2925, 1743, 1638, 1560, 1489, 1402, 1320, 1052, 762; δ_H (300 MHz, $CDCl_3$)* 2.74 [3H, s, C(3)CH$_3$], 3.34 [4H, br s, C(1')H$_2$ and C(2')H$_2$], 7.18 [1H, dd, *J* 7.5, 4.8, C(5")H], 7.61 [1H, dd, *J* 7.2, 1.8, C(4")H], 7.64–7.72 [2H, m, C(6)H and C(7)H], 7.94–8.05 [2H, m, C(5)H and C(8)H], 8.24 [1H, dd, *J* 4.8, 1.8, C(6")H]; δ_C (75.5 MHz, $CDCl_3$)** 22.8 [CH_3, C(3)CH_3], 33.1 [CH_2, C(1')H_2 or C(2')H_2], 34.7 [CH_2, C(1')H_2 or C(2')H_2], 122.9 [CH, C(5")H], 128.3, 128.5, 128.9, 129.1 [4 × CH, C(5)H, C(6)H, C(7)H, C(8)H], 138.0 [C, C(3")], 138.9 [CH, C(4")H], 140.9 and 141.0 [2 × C, quaternary bridgehead carbons C(4)a and C(8)a], 144.3 [C, C(2")Br], 148.0 [CH, C(6")H] 153.1 and 154.5 [2 × C, C(2) and C(3)]; HRMS (ES+): Exact mass calculated for $C_{16}H_{15}{}^{81}BrN_3$ $[M+H]^+$, 330.0429. Found 330.0428 and exact mass calculated for $C_{16}H_{15}{}^{79}BrN_3$ $[M+H]^+$, 328.0449. Found 328.0446. m/z (ES+) 330.2 {[$(C_{16}H_{15}{}^{81}BrN_3)^+$], 59%}, 328.2 {[$(C_{16}H_{15}{}^{79}BrN_3)^+$], 60%}.

Single crystals of 2-[2-(2-bromopyridin-3-yl)ethyl]-3-methylquinoxaline **232** were grown from deuterated chloroform. Crystal data: $C_{16}H_{14}BrN$, M = 328.21, monoclinic, $P2_1/c$, a = 8.4247(8) Å, b = 23.280(3) Å, c = 7.3012(8) Å, β = 95.430(4)°, V = 1425.5(3) Å^3, Z = 4, D_c = 1.529 g cm^{-3}, F_{000} = 664, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 27.17°, μ = 2.877 mm^{-1}, 16060 reflections collected, 3133 unique (R_{int} = 0.0307), final GooF = 1.028, R_1 = 0.0356, wR_2 = 0.0708 (2369 obs. data: $I > 2\sigma(I)$); R_1 = 0.0555, wR_2 = 0.0769 (all data). Full details are given in *Appendix III*.

* ^{1}H NMR spectrum contained an unknown signal δ_H ~4.6 ppm [1H, br s].
** ^{13}C NMR spectrum contains unknown C–H signal at δ_C 129.7 ppm and unknown CH_2 signal at δ_C 63.0 ppm as confirmed by DEPT 90/135 experiments.

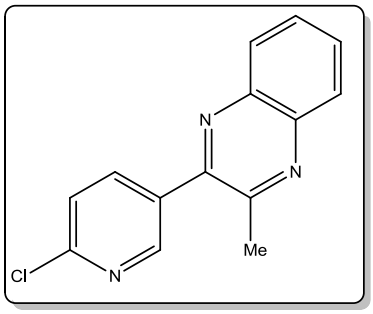
2-(2-Chloropyridin-3-yl)-3-methylquinoxaline 224



This was prepared following the procedure described for **229** (Method B: From non-purified 2,3-diketone), using α-diazoketone **64** (0.10 g, 0.51 mmol), singly distilled dichloromethane (40 mL), $Rh_2(OAc)_4$ (2.5 mg, 1 mol%) to provide the crude *2,3-diketone* as a brown/yellow oil (~90% pure by ^{1}H NMR); ν_{max}/cm^{-1} (film) 2920, 1717, 1694, 1577, 1400, 1082, 904, 666; δ_H (300 MHz, $CDCl_3$) 2.60 [3H, s, C(1)H$_3$], 7.43 [1H, dd, *J* 7.5, 4.8, C(5')H], 7.99 [1H, dd, *J* 7.5, 1.8, C(4')H], 8.59 [1H, dd, *J* 4.8, 2.1, C(6')H]. 1,2-Diaminobenzene **215** (0.12 g, 1.12 mmol) was added in one portion to a stirring solution of crude *2,3-diketone* in singly distilled dichloromethane (40 mL) to furnish the crude *quinoxaline* as a brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) followed by ethyl acetate/hexane (40:60) gave the pure *quinoxaline* **224** (0.09 g, 70%) as a yellow solid; m.p. 149–150 °C; (Found C, 65.26; H, 3.79; N, 16.31; Cl, 14.30. $C_{14}H_{10}ClN_3$ requires C, 65.76; H, 3.94; N, 16.43; Cl, 13.86%); ν_{max}/cm^{-1} (KBr) 2921, 1654, 1637, 1560, 1388, 1342, 1133, 1091, 999, 827, 753; δ_H (300 MHz, $CDCl_3$) 2.65 [3H, s, C(3)CH$_3$], 7.46 [1H, dd, *J* 7.5, 4.8, C(5')H], 7.74–7.87 [3H, m, C(4')H, C(6)H, C(7)H], 8.11 [2H, dt, *J* 8.4, 1.8, C(5)H and C(8)H], 8.58 [1H, dd, *J* 4.8,

1.8, C(6')H]; δ_C (75.5 MHz, $CDCl_3$) 23.0 [CH_3, C(3)CH_3], 122.8 [CH, C(5')H], 128.5, 129.2, 129.6, 130.6 [4 × CH, C(5)H, C(6)H, C(7)H, C(8)H], 134.6 [C, C(3')], 139.3 [CH, C(4')H], 140.5 and 141.9 [2 × C, quaternary bridgehead carbons C(4)a and C(8)a], 149.6 [C, C(2) or C(3)], 150.2 [CH, C(6')H], 151.3 [C(2) or C(3)], 152.7 [C, C(2')Cl]; HRMS (ES+): Exact mass calculated for $C_{14}H_{11}{}^{37}ClN_3$ $[M+H]^+$, 258.0612. Found 258.0607 and exact mass calculated for $C_{14}H_{11}{}^{35}ClN_3$ $[M+H]^+$, 256.0642. Found 256.0630. m/z (ES+) 258.1 {[$(C_{14}H_{11}{}^{37}ClN_3)^+$], 32%}, 256.1 {[$(C_{14}H_{11}{}^{35}ClN_3)^+$], 94%}.

2-(6-Chloropyridin-3-yl)-3-methylquinoxaline 225



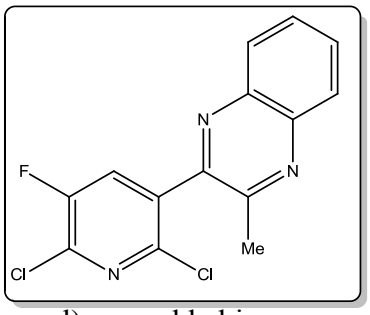
This was prepared following the procedure described for **229** (Method B: From non-purified 2,3-diketone), using α-diazoketone **63** (0.10 g, 0.51 mmol), singly distilled dichloromethane (40 mL) and $Rh_2(OAc)_4$ (2.5 mg, 1 mol%) to afford the crude *2,3-diketone* as a dark yellow/green oil (~90% pure by ^1H NMR); ν_{max}/cm^{-1} (film) 2926, 1718, 1686; δ_H (300 MHz, $CDCl_3$) 2.56 [3H, s, C(1)H_3], 7.48 [1H, finely split dd, *J* 8.4, 0.6, C(5')H], 8.34 [1H, dd, *J* 8.4, 2.4, C(4')H], 9.08 [1H, d, *J* 2.4, C(2')H]. 1,2-Diaminobenzene **215** (0.13 g, 1.21 mmol) was added in one portion to a stirring solution of crude *2,3-diketone* in singly distilled dichloromethane (40 mL) to give the crude *quinoxaline* as a pale brown solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) followed by ethyl acetate/hexane (40:60) provided the pure *quinoxaline* **225** (0.09 g, 58%) as a fluffy white solid; m.p. 184–185 °C; (Found C, 65.91; H, 4.01; N, 16.58; Cl, 13.92. $C_{14}H_{10}ClN_3$ requires C, 65.76; H, 3.94; N, 16.43; Cl, 13.86%); ν_{max}/cm^{-1} (KBr) 3054, 1654, 1637, 1584, 1560, 1468, 1459, 1374, 1340, 1194, 1114, 995, 859, 758, 744; δ_H (300 MHz, $CDCl_3$) 2.82 [3H, s, C(3)CH_3], 7.52 [1H, finely split dd, *J* 8.1, 0.6, C(5')H], 7.72–7.84 [2H, m, C(6)H and C(7)H], 8.02 [1H, dd, *J* 8.1, 2.4, C(4')H], 8.05–8.13 [2H, m, C(5)H and C(8)H], 8.75 [1H, finely split dd, *J* 2.7, 0.9, C(2')H]; δ_C (75.5 MHz, $CDCl_3$) 24.2 [CH_3, C(3)CH_3], 124.2 [CH, C(5')H], 128.5, 129.2, 129.8, 130.6 [4 × CH, C(5)H, C(6)H, C(7)H, C(8)H], 133.7 [C, C(3')], 139.3 [CH, C(4')H], 140.0 and 141.5 [2 × C, quaternary bridgehead carbons C(4)a and C(8)a], 149.9 [CH, C(2')H], 150.5 [C, C(2) or C(3)], 151.8 [C, C(6')Cl], 152.1 [C, C(2) or C(3)]; HRMS (ES+): Exact mass calculated for $C_{14}H_{11}{}^{37}ClN_3$ $[M+H]^+$, 258.0612. Found 258.0620 and exact mass calculated for $C_{14}H_{11}{}^{35}ClN_3$ $[M+H]^+$, 256.0642. Found 256.0640. m/z (ES+) 258.1 {[$(C_{14}H_{11}{}^{37}ClN_3)^+$], 32%}, 256.1 {[$(C_{14}H_{11}{}^{35}ClN_3)^+$], 90%}.

Method C: Preparation of quinoxaline **225** *using Cu(OTf)$_2$-catalysed one-pot coupling of a-diazoketone* **63** *and 1,2-diaminobenzene* **215**[230]

A mixture of α-diazoketone **63** (0.10 g, 0.51 mmol), 1,2-diaminobenzene **215** (0.05 g, 0.51 mmol) and copper(II) triflate (0.02 g, 10 mol%) in dichloroethane (10 mL) was stirred at 80 °C for 3 h under nitrogen. After completion of the reaction as indicated by TLC analysis and infrared spectroscopy, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). Concentration of the solvent provided the crude *quinoxaline* as a pale yellow solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) followed by ethyl acetate/hexane (40:60) furnished the purified *quinoxaline* **225** (0.02 g, 15%)* as a bright yellow solid. Spectral properties were consistent with those obtained for **225** above using method B: Generation of 2,3-diketones from α-diazoketones without purification and subsequent condensation with 1,2-diaminobenzene **215**.

* ^{1}H NMR spectrum contains ~12% co-eluting unknown product.

2-(2,6-Dichloro-5-fluoropyridin-3-yl)-3-methylquinoxaline 226



This was prepared following the procedure described for **229** (Method B: From non-purified 2,3-diketone), using α-diazoketone **65** (0.10 g, 0.42 mmol), singly distilled dichloromethane (40 mL) and $Rh_2(OAc)_4$ (4.1 mg, 1 mol%) to provide the crude *2,3-diketone* as a yellow oil (~80–90% pure by ^{1}H NMR); ν_{max}/cm^{-1} (film) 2923, 1715, 1590, 1556, 1402, 1126, 1059; δ_H (300 MHz, $CDCl_3$) 2.59 [3H, s, C(1)$\underline{H}_3$], 7.79 [1H, d, *J* 6.9, C(4')$\underline{H}$]. 1,2-Diaminobenzene **215** (0.75 g, 0.70 mmol) was added in one portion to a stirring solution of crude *2,3-diketone* in singly distilled dichloromethane (40 mL) to afford the crude *quinoxaline* as an orange solid. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60) gave the pure *quinoxaline* **226** (0.06 g, 48%) as an orange/yellow solid; m.p. 137–139 °C; (Found C, 54.10; H, 2.65; N, 13.43. $C_{14}H_8Cl_2FN_3$ requires C, 54.57; H, 2.62; N, 13.64%); ν_{max}/cm^{-1} (KBr) 2930, 1654, 1637, 1617, 1560, 1385, 1080, 774, 668; δ_H (300 MHz, $CDCl_3$) 2.68 [3H, s, C(3)C$\underline{H}_3$], 7.66 [1H, d, J_{HF} 6.9, C(4')$\underline{H}$], 7.76–7.89 [2H, m, C(6)$\underline{H}$ and C(7)$\underline{H}$], 8.06–8.14 [2H, m, C(5)$\underline{H}$ and C(8)$\underline{H}$]; δ_C (75.5 MHz, $CDCl_3$) 22.8 [CH_3, C(3)$\underline{C}H_3$], 127.8 [CH, d, $^2J_{CF}$ 21.0, $\underline{C}$(4')H], 128.6, 129.2, 130.0, 131.1 [4 × CH, $\underline{C}$(5), $\underline{C}$(6)H, $\underline{C}$(7)H, $\underline{C}$(8)H], 134.9 [C, d, $^3J_{CF}$ 2.8, $\underline{C}$(3')], 138.5 [C, d, $^2J_{CF}$ 21.1, $\underline{C}$(6')Cl], 140.4 and 142.1 [2 × C, quaternary bridgehead carbons $\underline{C}$(4)a and $\underline{C}$(8)a], 142.7 [C, d, $^4J_{CF}$, 3.5, $\underline{C}$(2')Cl], 149.0 and 152.2 [2 × C, $\underline{C}$(2) and $\underline{C}$(3)], 154.2 [C, d, $^1J_{CF}$ 263.9, $\underline{C}$(5')F]; HRMS (ES+): Exact mass calculated for $C_{14}H_9{}^{37}Cl^{35}ClFN_3$, $[M+H]^+$, 310.0128. Found 310.0117 and exact mass calculated for $C_{14}H_9{}^{35}Cl_2FN_3$ $[M+H]^+$, 308.0158. Found 308.0145. m/z (ES+)* 309.9 {$[(C_{14}H_8{}^{37}Cl^{35}ClFN_3)^+]$, 34%}, 307.9 {$[(C_{14}H_8{}^{35}Cl_2FN_3)^+]$, 100%}.

Note: One-pot copper(II) triflate-catalysed coupling of α-diazoketones with 1,2-diamines as outlined by Yadav et al.[230] *was attempted on α-diazoketone* **65** *but analysis of crude product by TLC indicated a complex mixture of products and no purification was attempted on this sample.*

* Molecular formula incorrectly entered in the nominal mass spectrometric analysis as molecular formula should be m/z (ES+) $[(C_{14}H_9{}^{37}Cl^{35}ClFN_3)^+]$ and $[(C_{14}H_9{}^{35}Cl_2FN_3)^+]$.

(ii) Rhodium(II)-catalysed reactions under Schlenk conditions

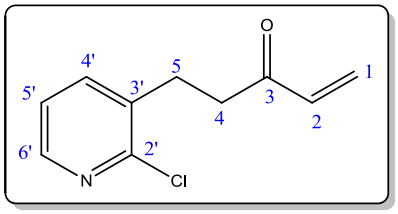
General procedure for Schlenk conditions in rhodium(II)- and copper(II)-catalysed reactions

A three necked round-bottom flask was fitted with a pressure equalising addition funnel and condenser (in case of reaction heated under reflux). The glassware was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane was added to the flask. The Schlenk stopcock was opened. The vacuum/inert manifold was opened to the vacuum for 20 seconds. The vacuum/inert gas manifold was then opened to the nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. The rhodium(II) or copper(II) catalyst was added at this point to the solvent and the system was again evacuated and refilled with nitrogen and stirred for 1 h at rt or heated under reflux for 3 h. A solution of α-diazoketone in doubly distilled dichloromethane was added dropwise over ~1 h to a stirring solution at rt/reflux. The reaction

mixture was stirred at rt/heated under reflux until infrared analysis confirmed consumption of starting material and completion of reaction. In cases where two portions of the rhodium catalyst were added (*i.e.* 2 × 1 mol%), the second portion was introduced following addition of half of the α-diazoketone solution to the catalyst/solvent mixture.

The purpose of carrying out cyclisations under these stringent conditions is to saturate the atmosphere with nitrogen preventing the unwanted side reaction of molecular oxygen with metallocarbenoid to generate the 2,3-diketone, as seen previously. Flame drying all glassware prior to reaction helps eliminate adventitious water from reacting with metallocarbenoid to generate the α-hydroxyketone.

5-(2-Chloropyridin-3-yl)pent-1-en-3-one 237

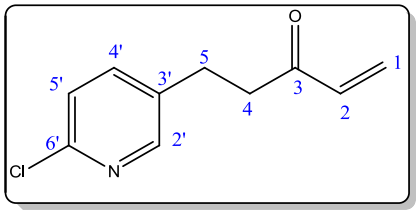


A solution of α-diazoketone **134** (0.16 g, 0.70 mmol) in doubly distilled dichloromethane (5 mL) was added dropwise over 30 min to a stirring solution of rhodium(II) perfluorobutyrate [$Rh_2(pfb)_4$, (2 × 1 mg, 2 × 1 mol%)] in doubly distilled dichloromethane (3 mL) under Schlenk conditions at room temperature. The reaction mixture was stirred overnight at room temperature. Analysis of the reaction mixture by TLC and infrared spectroscopy showed consumption of the starting material after 18 h. Removal of solvent under reduced pressure afforded the crude product as a brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) to (40:60) gave the *enone* **237** (0.01 g, 9%) as a colourless oil which co-eluted with *2,3-diketone* **209** in a ratio of **237** : **209** 57 : 43; ν_{max}/cm^{-1} (film) 2927, 1719, 1656, 1411, 124; δ_H (400 MHz, $CDCl_3$) 2.29 [2.3H, s, C(1)$\underline{H}_3$ of diketone], 2.87–3.03 [6H, m, C(4)$\underline{H}_2$ and C(5)$\underline{H}_2$ of enone and C(4)$\underline{H}_2$ of diketone], 3.09 [1.5H, *J* 7.2, C(5)$\underline{H}_2$ of diketone], 5.80 [1H, dd, *J* 10.2, 1.5, one of C(1)$\underline{H}_2$ of enone], 6.17 [1H, dd, *J* 17.7, 1.5, one of C(1)$\underline{H}_2$ of enone], 6.29 [1H, dd, *J* 17.7, 9.9, C(2)$\underline{H}CH_2$ of enone], 7.07–7.16 [1.9H, m, C(5')$\underline{H}$ of enone and diketone], 7.56 [1.9H, ddd, *J* 7.5, 5.7, 2.1, C(4')$\underline{H}$ of enone and diketone], 8.20 [1.8H, ddd, *J* 6.0, 4.2, 1.8, C(6')$\underline{H}$ of enone and diketone].

* Identification of 2,3-diketone **209** was aided by comparison with sample isolated previously in this work.

Note: Formation of the terminal enone **237** was also achieved under Schlenk conditions at room temperature using $Rh_2(OAc)_4$ as catalyst. The purified enone **237** co-eluted with 2,3-diketone **209** and was isolated as an impure sample in 29% yield**.** The ratio of **237** : **209** was 78 : 22.

5-(6-Chloropyridin-3-yl)pent-1-en-3-one 239



A solution of α-diazoketone **135** (0.11 g, 0.51 mmol) in doubly distilled dichloromethane (10 mL) was added dropwise over 30 min to a refluxing solution of $Rh_2(pfb)_4$ (5.4 mg, 2 mol%) in doubly distilled dichloromethane (15 mL) under Schlenk conditions. The reaction mixture was heated under reflux overnight. Analysis of the reaction mixture by TLC and infrared spectroscopy showed consumption of the starting material after 18 h. Removal of solvent under reduced pressure afforded the crude product as a brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to

(20:80) to (40:60) gave the *enone* **239** (0.01 g, 5%) as a colourless oil which co-eluted with *2,3-diketone* **210*** in a ratio of **239** : **210** 84 : 16. A more polar compound, Unknown A **240** (0.03 g), was also isolated as a white solid. Colourless oil; ν_{max}/cm^{-1} (film) 2925, 1719, 1702, 1686, 1654, 1560, 1460; δ_H (400 MHz, $CDCl_3$) 2.33 [0.6H, s, C(1)$\underline{H}_3$ of diketone], 2.87–2.99 [5H, m, C(4)$\underline{H}_2$, C(5)$\underline{H}_2$ of enone and C(4)$\underline{H}_2$ of diketone], 3.10 [0.4H, t, *J* 7.2, C(5)$\underline{H}_2$ of diketone], 5.86 [1H, dd, *J* 10.6, 0.8, one of C(1)$\underline{H}_2$ of enone], 6.22 [1H, dd, *J* 17.2, 0.8, one of C(1)$\underline{H}_2$ of enone], 6.36 [1H, dd, *J* 17.6, 10.6, C(2)$\underline{H}CH_2$ of enone], 7.24–7.28** [1.7H, br s overlapping with $CDCl_3$, C(5')$\underline{H}$ of enone and diketone], 7.53 [1.7H, br s with further unresolved splitting, C(4')$\underline{H}$ of enone and diketone], 8.27 [1.5H, br s with further unresolved splitting, C(6')$\underline{H}$ of enone and diketone]; HRMS (ES+): Exact mass calculated for $C_{10}H_{11}{}^{35}ClNO$ $[M+H]^+$, 196.0529. Found 196.0521. m/z (ES+) 198.3 {$[(C_{10}H_{11}{}^{37}ClNO)^+]$, 12%}, 196.3 {$[(C_{10}H_{11}{}^{35}ClNO)^+]$, 32%}.

Unknown A **240**, white solid***; ν_{max}/cm^{-1} (film) 2927, 1718, 1560, 1460, 1388, 1108; δ_H (400 MHz, $CDCl_3$) 1.34 [1.4H, d, *J* 7.2], 1.75–1.86 [1.7H, m], 2.06–2.16 [1.5H, m], 2.19 [3H, s], 2.70–2.98 [4.6H, m], 4.13 [1.4H, m contains dd and d], 7.25 [2.5H, dd, *J* 8.0, 6.4], 7.50 [1.6H, apparent ddd, *J* 14.0, 8.0, 2.4], 8.25 [1.5H, apparent dd, *J* 8.0, 2.4].

* Identification of 2,3-diketone **210** was aided by comparison with sample isolated earlier in this work.
** Integration is higher than expected due to overlap with $CDCl_3$.
*** Signals for the white solid could be tentatively ascribed to a possible O–H insertion product but identification is not definitive.
Note: On repeating the reaction under Schlenk conditions at room temperature, in the presence of $Rh_2(pfb)_4$, the 2,3-diketone **210** was isolated as the major product.

(iii) Spiking studies in rhodium(II)-catalysed reactions using pyridine and 2,6-dichloropyridine

General procedure for spiking studies involving intermolecular cyclopropanation and intermolecular aromatic addition

The rhodium(II)-mediated transformations of **243** and **245** were carried out under four different reaction conditions with the order of addition of the components specific for each of the conditions, termed Experiments A, B, C and D. In all cases, the crude samples were not further purified and the pertinent infrared and ^1H NMR spectroscopic data was deemed sufficient to establish if desired reaction pathway had successfully taken place.

The Experiments A–D were as follows;

- Experiment A: The blank reaction of $Rh_2(OAc)_4$, styrene (if applicable) and α-diazoketone/α-diazoacetate conducted by placing the rhodium catalyst (1 mol%) and styrene (10 equiv.) in dichloromethane followed by dropwise addition (15–20 min) of a solution of **243** or **245** in dichloromethane to the reaction mixture at room temperature. The reaction was complete within 1 h by TLC and infrared monitoring.

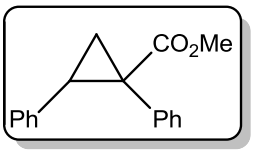
- Experiment B: The $Rh_2(OAc)_4$ catalyst and styrene (if applicable) were placed in dichlorometane followed by addition of the α-diazoketone/α-diazoacetate. Once the

addition of **243** or **245** was complete, the reaction was stirred for 5 min and then pyridine (1.0 equiv. relative to **243** or **245**) was added to the reaction mixture.

- Experiment C: The $Rh_2(OAc)_4$ catalyst and styrene (if applicable) were placed in dichlormethane followed in this case by addition of pyridine (1.0 equiv.). The reaction mixture stirred for 5 min prior to addition of **243** or **245**.

- Experiment D: The $Rh_2(OAc)_4$ catalyst and styrene (if applicable) were placed in dichloromethane followed by addition 2,6-dichloropyridine (1.0 equiv. relative to the **243** or **245**) in place of pyridine. The reaction mixture was stirred for 5 min before addition of the **243** or **245**.

Methyl 1,2-diphenylcyclopropanecarboxylate 244 from intermolecular cyclopropanation of styrene by 243



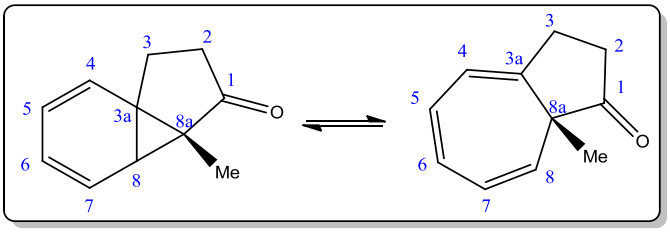
A mixture of doubly distilled dichloromethane (6 mL) and $Rh_2(OAc)_4$ (2.8 mg, 1 mol%) and styrene (0.7 mL, 5.67 mmol) was stirred at room temperature. To the reaction mixture was added methyl 2-diazo-2-phenylacetate **243** (prepared in **Section 3.3.1.3**, 0.10 g, 0.57 mmol) and pyridine (0.05 mL, 0.57 mmol) or 2,6-dichloropyridine (0.08 g, 0.57 mmol) with the order of addition dependent on the Experiments A, B, C or D employed. The reaction mixture was stirred at room temperature and the reaction progress was monitored by infrared and ^{1}H NMR spectroscopy. After stirring at room temperature for 1 h, the reaction was found to be complete. The reaction mixture was concentrated under reduced pressure to afford the crude *cyclopropane* **244** as a colourless oil; ν_{max}/cm^{-1} (film) 1720, 1438, 1260; Characteristic signals for **244** δ_H (400 MHz, $CDCl_3$) 1.88 [1H, dd, *J* 7.6, 4.8, one of C$\underline{H}_2$ cyclopropane], 2.13 [1H, dd, *J* 9.2, 4.8, one of C$\underline{H}_2$ cyclopropane], 3.11 [1H, dd, *J* 9.2, 7.6, PhC$\underline{H}$], 3.66 [3H, s, OC$\underline{H}_3$]. Spectral properties were consistent with the literature,[299,300] as well as data obtained elsewhere in this work (**Section 3.3.1.3**).

Table 2.21: *Mass recovery and characteristic infrared stretching frequencies from attempted cyclopropanation of* ***243***

Entry	Substrate	Experiment	ν_{max}/ cm^{-1}	Reaction progress[a]	Mass recovery (%)[b]	Diazo 243	Cyclopropane 244
1	**243**	A	1720	✓	41	×	✓
2	**243**	B	1720	✓	17	×	✓
3	**243**	C	2091	×	–[c]	✓	×
4	**243**	D	1717	✓	41	×	✓

[a] Reaction progress monitored by infrared and ^{1}H NMR spectroscopy of the crude products.
[b] Mass recovery in crude-contains **244** and styrene.
[c] For Experiment C, only starting material **243** was recovered as the reaction was not catalysed.

3,8a-Dihydro-8a-methylazulen-1(2*H*)-one 246 from intramolecular aromatic addition reaction of 245



A mixture of doubly distilled dichloromethane (6 mL) and $Rh_2(OAc)_4$ (2.6 mg, 1 mol%) was stirred at room temperature. To the reaction mixture was added methyl 4-diazo-1-phenylpentan-3-one **245**[167] and pyridine (0.04 mL, 0.53 mmol) or 2,6-dichloropyridine (0.08 g, 0.53 mmol) with the order of addition dependent on the method a, b, c or d employed. The reaction mixture was stirred at room temperature and the reaction progress was monitored by infrared and ^{1}H NMR spectroscopy. After stirring at room temperature for 1 h, the reaction was found to be complete. The reaction mixture was concentrated under reduced pressure to furnish the crude *azulenone* **246** as a pale yellow oil; ν_{max}/cm^{-1} (film) 2929, 1715, 1454, 1249; Characteristic ^{1}H NMR signals for **246** δ_H (400 MHz, $CDCl_3$) 4.25 [1H, d, *J* 8.3, C(8)H], 6.07–6.21 [2H, m, two of C(4)H, C(5)H, C(6)H, C(7)H], 6.26–6.35 [2H, m, two of C(4)H, C(5)H, C(6)H, C(7)H]. Spectral properties were consistent with previously reported data in the Maguire group.[12]

Table 2.22: *Mass recovery and characteristic infrared stretching frequencies from attempted aromatic addition of* ***245***

Entry	Substrate	Experiment	ν_{max}/cm^{-1}	Reaction progress[a]	Mass recovery (%)[b]	Diazo 245	CHT 246
1	**245**	A	1715	✓	quant.	×	✓
2	**245**	B	1714	✓	quant.	×	✓
3	**245**	C	2074	×	–[c]	✓	×
4	**245**	D	1713	✓	quant.	×	✓

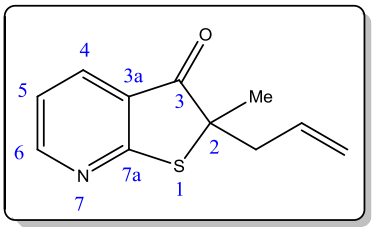
[a] Reaction progress monitored by infrared and ^{1}H NMR spectroscopy of the crude product.
[b] Mass recovery in crude-contains **246.**
[c] For Experiment C, only starting material **245** was recovered as the reaction was not catalysed.

(iv) Ylide formation/rearrangement and attempted C–H insertion reactions

General procedure for rhodium(II)- and copper(II)-catalysed ylide formation/rearrangement

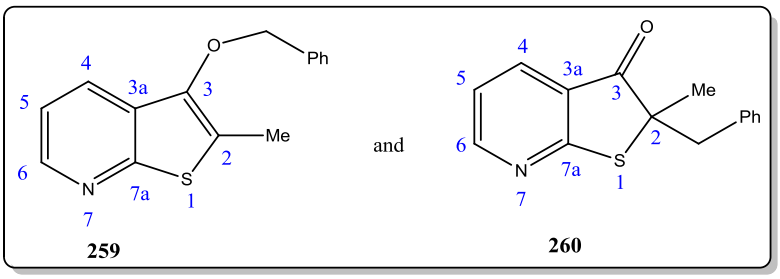
A solution of α-diazoketone (0.08 g, 1 equiv.) in doubly distilled dichloromethane (20 mL, further degassed using freeze, pump, thaw technique) was added dropwise over ~1 h to a refluxing solution of doubly distilled dichloromethane (40 mL) and catalyst, [rhodium (2 mol%) or copper (10 mol%)]. The catalyst/solvent mixture was heated under reflux for 3 h under Schlenk conditions prior to addition of the α-diazoketone. The reaction mixture was heated under reflux while stirring until infrared analysis confirmed consumption of starting material and completion of reaction. The reaction mixture was then cooled to room temperature and concentrated *in vacuo* to give the crude product. Purification by column chromatography using ethyl acetate/hexane (10:90) to (20:80) as eluent afforded the purified ylide formation/rearrangement and/or C–H insertion products.

2-Allyl-2-methylthieno[2,3-b]pyridin-3(2*H*)-one 256



A solution of α-diazoketone **144** (0.82 g, 0.35 mmol) in doubly distilled dichloromethane (10 mL) was added dropwise over 30 min to a refluxing solution of copper(II) acetylacetonate [$Cu(acac)_2$] (0.01 g, 10 mol%) in doubly distilled dichloromethane (40 mL) under Schlenk conditions. The reaction mixture was heated under reflux and stirred overnight. The progress of the reaction was monitored by infrared analysis was found to be complete after 18 h. Concentration of sample under reduced pressure yielded the crude product as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) furnished the pure *[2,3]-rearrangement product* **256** (0.06 g, 84%) as a yellow oil; ν_{max}/cm^{-1} (film) 3078, 2978, 2928, 1701, 1582, 1561, 1457, 1396, 1284, 1256, 1091, 924, 762; δ_H (400 MHz, $CDCl_3$) 1.61 [3H, s, C(2)C$\underline{H}_3$], 2.61 [2H, d, *J* 7.2, C(2)C$\underline{H}_2$CHCH_2], 5.10 [1H, d with further unresolved splitting, *J* 10.0, one of C(2)CH_2CHC$\underline{H}_2$], 5.16 [1H, dd with further unresolved splitting, *J* 15.2, 1.2, one of C(2)CH_2CHC$\underline{H}_2$], 5.70–5.83 [1H, m, C(2)CH_2C$\underline{H}$CH_2], 7.13 [1H, dd, *J* 7.6, 4.8, C(5)$\underline{H}$], 7.94 [1H, dd, *J* 7.6, 1.6, C(4)$\underline{H}$], 8.66 [1H, d with further unresolved splitting, *J* 4.8, C(6)$\underline{H}$]; δ_C (125.8 MHz, $CDCl_3$); 24.7 [CH_3, C(2)$\underline{C}H_3$], 43.5 [CH_2, C(2)$\underline{C}H_2$CHCH_2], 63.1 [C, $\underline{C}$(2)], 118.0 [CH, $\underline{C}$(5)H], 120.3 [CH_2, C(2)CH_2CH$\underline{C}H_2$], 124.5 [C, $\underline{C}$(3a)], 132.0 [CH, C(2)$CH_2\underline{C}$HCH_2 or $\underline{C}$(4)H], 134.7 [CH, C(2)$CH_2\underline{C}$HCH_2 or $\underline{C}$(4)H], 156.8 [CH, $\underline{C}$(6)H], 173.0 [C, $\underline{C}$(7a)], 203.2 [C, $\underline{C}$(3)=O]; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NOS$ $[M+H]^+$, 206.0640. Found 206.0632. m/z (ES+) 206.3 $[(M+H)^+$, 100%].

3-(Benzyloxy)-2-methylthieno[2,3-b]pyridine 259 and 2-benzyl-2-methylthieno[2,3-b]pyridin-3(2*H*)-one 260



A solution of α-diazoketone **143** (0.10 g, 0.36 mmol) in doubly distilled dichloromethane (15 mL) was added dropwise over 30 min to a refluxing solution of $Cu(hfacac)_2$ (0.013 g, 10 mol%) in doubly distilled dichloromethane (40 mL) under Schlenk conditions. The reaction mixture was heated under reflux overnight with the reaction going to completion after 18 h. Removal of excess solvent under reduced pressure gave the crude product as a green/yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) to (15:85) gave the purified products. The less polar compound, a pale yellow oil (0.03 g, 33%), was assigned as **259** and the more polar compound, a colourless oil (0.01 g, 13%) was assigned as **260**; {[1,4]-shift product} **259**; ν_{max}/cm^{-1} (film) 2912, 1655, 1579, 1458, 1391, 1377, 1345, 1115, 1088; δ_H (400 MHz, $CDCl_3$) 2.34 [3H, s, C(2)C$\underline{H}_3$], 5.05 [2H, s, C(3)OC$\underline{H}_2C_6H_5$], 7.23 [1H, dd, *J* 8.0, 4.4, C(5)$\underline{H}$], 7.36–7.41 [5H, m, 5 × aromatic $\underline{H}$], 7.83 [1H, dd, *J* 8.0, 1.2, C(4)$\underline{H}$], 8.48 [1H, unresolved br s, C(6)$\underline{H}$]; δ_C (125.8 MHz, $CDCl_3$) 11.9 [CH_3, C(2)$\underline{C}H_3$], 75.9 [CH_2, C(3)O$\underline{C}H_2C_6H_5$], 119.1 [CH, $\underline{C}$(5)H], 125.8 [C, $\underline{C}$(2) or $\underline{C}$(3a)], 127.6 [CH, $\underline{C}$(4)H], 127.9 [C, $\underline{C}$(2) or $\underline{C}$(3a)], 128.5 [CH, 3 × aromatic $\underline{C}$H, 2 × overlapping signals], 128.6 [CH, 2 × aromatic $\underline{C}$H], 136.9 [C, aromatic $\underline{C}$], 143.4 [C, $\underline{C}$(7a)], 146.1 [CH, $\underline{C}$(6)H],

157.3 [C, C(3)$OCH_2C_6H_5$]; HRMS (ES+): Exact mass calculated for $C_{15}H_{14}NOS$ $[M+H]^+$, 256.0796. Found 256.0793. m/z (ES+) 256.3 $[(M+H)^+$, 100%].

{[1,2]-shift product} **260***; ν_{max}/cm^{-1} (film) 1698, 1654, 1638, 1581, 1561, 1458, 1396, 1286; δ_H (400 MHz, $CDCl_3$) 1.62 [3H, s, C(2)CH_3], 3.13 [1H, A of AB, *J* 13.6, one of C(2)$CH_2C_6H_5$], 3.18 [1H, B of AB, *J* 13.6, one of C(2)$CH_2C_6H_5$], 7.09 [1H, dd, *J* 7.6, 4.8, C(5)H], 7.18–7.30 [5H, m, 5 × aromatic H], 7.92 [1H, dd, *J* 8.0, 2.0, C(4)H], 8.62 [1H, dd, *J* 4.8, 2.0, C(6)H]; δ_C (125.8 MHz, $CDCl_3$) 24.8 [CH_3, C(2)CH_3], 45.0 [CH_2, C(2)$CH_2C_6H_5$], 64.4 [C, C(2)], 119.6 [CH, C(5)H], 124.5 [C, C(3a)], 127.2 [CH, aromatic CH], 128.1 [CH, 2 × aromatic CH], 130.6 [CH, 2 × aromatic CH], 134.6 [CH, C(4)H], 135.6 [C, aromatic C], 156.8 [CH, C(6)H], 172.9 [C, C(7a)], 203.4 [C, C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{15}H_{14}NOS$ $[M+H]^+$, 256.0796. Found 256.0792. m/z (ES+) 256.3 $[(M+H)^+$, 100%].

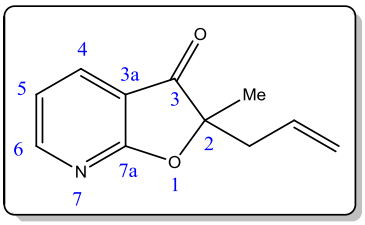
* Analysis for **260** is from reaction in the presence of $Rh_2(OAc)_4$ (**Table 2.23**, entry 3).

Table 2.23 *Transition metal-catalysed sulfonium ylide/rearrangement of 1-[2-(benzylthio)pyridin-3-yl]-2-diazopropan-1-one* **143**[a]

Entry	Catalyst	Time (h)	259 : 260[b]	259 (%)[c]	260 (%)[c]
1	$Cu(hfacac)_2$	18	76 : 24	33	13
2	$Cu(acac)_2$	21	77 : 23	19	5
3	$Rh_2(OAc)_4$	18	75 : 25	37	12
4	$Rh_2(pfb)_4$	18	75 : 25	38	8

[a] Reactions conducted using the general procedure for rhodium(II)- and copper(II)-catalysed C–H insertion or ylide formation/rearrangement reactions.
[b] Ratio of **259** : **260** established by integration of benzylic CH_2 signals in crude ^1H NMR spectrum.
[c] Isolated yields of products after column chromatography.

2-Allyl-2-methylfuro[2,3-b]pyridin-3(2*H*)-one 261

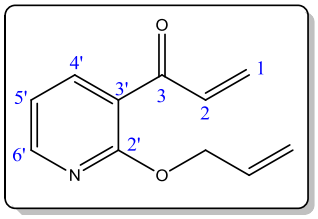


A solution of α-diazoketone **140** (0.10 g, 0.460 mmol) in doubly distilled dichloromethane (10 mL) was added dropwise over 30 min to a refluxing solution of $Cu(acac)_2$ (0.012 g, 10 mol%) in doubly distilled dichloromethane (40 mL) under Schlenk conditions. The reaction mixture was heated under reflux and the reaction was found to be complete after 40 h. Removal of solvent under reduced pressure gave the crude product as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) to (20:80) gave the pure *[2,3]-rearrangement product* **261** (0.03 g, 35%) as a yellow oil; ν_{max}/cm^{-1} (film) 2983, 1726, 1605, 1594, 1479, 1417, 1266, 1098, 930, 786; δ_H (400 MHz, $CDCl_3$) 1.49 [3H, s, C(2)CH_3], 2.60 [2H, dd, *J* 7.2, 1.2, C(2)CH_2CHCH_2], 5.06 [1H, d with further unresolved splitting, *J* 10.4, one of C(2)CH_2CHCH_2], 5.15 [1H, dd with further unresolved splitting, *J* 16.8, 1.6, one of C(2)CH_2CHCH_2], 5.62–5.74 [1H, m, C(2)CH_2CHCH_2], 7.08 [1H, dd, *J* 7.2, 4.8, C(5)H], 7.99 [1H, dd, *J* 7.2, 2.0, C(4)H], 8.57 [1H, dd, *J* 5.2, 2.0, C(6)H]; δ_C (125.8 MHz, $CDCl_3$) 21.2 [CH_3, C(2)CH_3], 40.9 [CH_2, C(2)CH_2CHCH_2], 90.4 [C, C(2)], 113.0 [C, C(3a)], 118.4 [CH, C(5)H], 120.4 [CH_2, C(2)CH_2CHCH_2], 130.2 [CH, C(2)CH_2CHCH_2 or C(4)H], 134.7 [CH, C(2)CH_2CHCH_2 or C(4)H], 157.7 [CH, C(6)H], 175.5 [C, C(7a)], 201.7 [C, C(3)=O]; HRMS (ES+): Exact mass

calculated for $C_{11}H_{12}NO_2$ $[M+H]^+$, 190.0868. Found 190.0859. m/z (ES+) 190.3 $[(M+H)^+$, 100%].

Isolated 1,2-hydride shift product from $Rh_2(pfb)_4$-catalysed reaction of α-diazoketone 140

3-[2-(Allyloxy)pyridin-3-yl]prop-1-en-3-one 263



α-Diazoketone **140** (0.08 g, 0.35 mmol) and $Rh_2(pfb)_4$(4.0 mg, 2 mol%) in doubly distilled dichloromethane (40 mL) were employed following the general procedure. Following chromatographic purification the *enone* **263** was isolated as a bright yellow oil (0.04 g, 55%) in addition to *2,3-rearrangement product* **261** as a colourless oil (0.02 g, 25%) which co-eluted with an unknown component. *Enone* **263**; ν_{max}/cm^{-1} (film) 2918, 1670, 1607, 1582, 1461, 1432, 1417, 1307, 1245, 1000; δ_H (400 MHz, $CDCl_3$) 4.96 [2H, dt, *J* 5.6, 1.2, $OC\underline{H}_2CHCH_2$], 5.26 [1H, dd with further unresolved splitting, *J* 10.4, 1.2, one of $OCH_2CHC\underline{H}_2$], 5.41 [1H, dd with further unresolved splitting, *J* 17.2, 1.6, one of $OCH_2CHC\underline{H}_2$], 5.83 [1H, dd, *J* 10.4, 1.6, one of $CHC(1)\underline{H}_2$], 6.03–6.15 [1H, m, $OCH_2C\underline{H}CH_2$], 6.37 [1H, dd, *J* 17.2, 1.6, one of $CHC(1)\underline{H}_2$], 7.00 [1H, dd, *J* 7.6, 4.8, C(5')H], 7.18 [1H, dd, *J* 17.2, 10.4, $C(2)\underline{H}CH_2$], 8.00 [1H, dd, *J* 7.6, 2.0, C(4')H], 8.29 [1H, dd, *J* 4.8, 2.0, C(6')H]; δ_C (75.5 MHz, $CDCl_3$)* 67.0 [CH_2, $O\underline{C}H_2CHCH_2$], 117.2 [CH, C(5')H], 117.5 [CH_2, $OCH_2CH\underline{C}H_2$], 128.9 [CH_2, $CH\underline{C}(1)H_2$], 129.7 [CH, $\underline{C}(2)HCH_2$ or $OCH_2\underline{C}HCH_2$], 132.9 [C, C(3')], 135.6 [CH, $\underline{C}(2)HCH_2$ or $OCH_2\underline{C}HCH_2$], 140.2 [CH, C(4')H], 150.4 [CH, C(6')H], 201.3 [C, C(3)=O]; HRMS (ES+): Exact mass calculated for $C_{11}H_{12}NO_2$ $[M+H]^+$, 190.0868. Found 190.0861. m/z (ES+) 190.3 $[(M+H)^+$, 100%].

* Signal for $\underline{C}(2')OCH_2CHCH_2$ not observed in ^{13}C NMR spectrum.

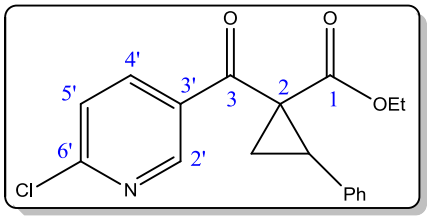
Table 2.24 *Transition metal-catalysed reaction of 1-[2-(allyloxy)pyridin-3-yl]-2-diazopropan-1-one* **140**; *oxonium ylide/rearrangement* **261** *and enone* **263**[a]

Entry	Catalyst	Time (h)	261 (%)[b]	263 (%)[b]
1	$Cu(hfacac)_2$	60	39[c]	–
2	$Cu(acac)_2$	42	35	–
3	$Rh_2(OAc)_4$	18	–[d]	–
4	$Rh_2(pfb)_4$	18	25[e]	55

[a] Reaction conducted using general procedure for rhodium(II)- and copper(II)-catalysed intramolecular C–H insertions or ylide formation/rearrangement reactions.
[b] Isolated yields of products after column chromatography.
[c] Unknown minor product co-eluted with rearrangement product resulting in a higher yield.
[d] There is possible evidence of 2,3-diketone with appearance of a singlet in ^1H NMR of purified product at δ_H 2.46 ppm. However, there is no evidence of formation of **261** or **263**.
[e] Sample isolated is impure and contains a mixture of **261** and an unknown component in essentially equimolar ratio.

(v) Intermolecular cyclopropanation

Ethyl 1-(6-chloronicotinoyl)-2-phenylcyclopropanecarboxylate 278



A solution of α-diazo-β-ketoester **157** (0.15 g, 0.59 mmol) in doubly distilled dichloromethane (3 mL) was added dropwise over 40 min to a stirring solution of $Rh_2(OAc)_4$ (0.02 g, 5 mol%) and styrene (6.8 mL, 5.91 mmol) in doubly distilled dichloromethane (3 mL) at room temperature under Schlenk conditions. The reaction mixture was stirred overnight at room temperature. Analysis of the reaction mixture by TLC and infrared spectroscopy showed consumption of the starting material after 18 h. Removal of solvent by evaporation furnished the crude cyclopropane as a red/brown oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (0:100) followed by (10:90), (20:80) and (40:60) gave the purified *cyclopropane* **278** (0.07 g, 34%) as a colourless oil which following crystallisation *via* slow evaporation from dichloromethane and hexane was isolated as a white solid; m.p. 60–62 °C; ν_{max}/cm^{-1} (KBr) 2980, 1735, 1686, 1580, 1454, 1363, 1310, 1277, 1149, 1106; δ_H (300 MHz, $CDCl_3$)* 0.73 [3H, t, *J* 6.9, $CH_2C\underline{H}_3$], 1.75 [1H, dd, *J* 9.3, 5.1, one of $C\underline{H}_2$ of cyclopropane ring], 2.49 [1H, dd, *J* 8.1, 4.8, one of $C\underline{H}_2$ of cyclopropane ring], 3.58 [1H, dd, *J* 9.0, 8.4, PhC<u>H</u>] 3.63–3.86 [2H, m, $C\underline{H}_2CH_3$], 7.19–7.35 [5H, m, 5 × aromatic <u>H</u>], 7.44 [1H, finely split dd, *J* 8.4, 0.6, C(5')<u>H</u>], 8.13 [1H, dd, *J* 8.4, 2.4, C(4')<u>H</u>], 8.89 [1H, finely split dd, *J* 2.4, 0.6, C(2')<u>H</u>]; δ_C (75.5 MHz, $CDCl_3$) 13.5 [CH_3, $CH_2\underline{C}H_3$], 20.4 [CH_2, $\underline{C}H_2$ of cyclopropane ring], 31.4 [CH, Ph<u>C</u>H], 42.2 [C, <u>C</u>(2)], 61.5 [CH_2, $\underline{C}H_2CH_3$], 124.4 [CH, <u>C</u>(5')H], 127.5 [CH, aromatic <u>C</u>H], 128.2 [CH, 2 × aromatic <u>C</u>H], 129.2 [CH, 2 × aromatic <u>C</u>H], 131.7 [C, aromatic <u>C</u> or <u>C</u>(3')], 134.1 [C, aromatic <u>C</u> or <u>C</u>(3')], 138.1 [CH, <u>C</u>(4')H], 149.7 [CH, <u>C</u>(2')H], 155.3 [C, <u>C</u>(6')Cl], 167.7 [C, <u>C</u>(1)=O], 192.2 [C, <u>C</u>(3)=O]; HRMS (ES+): Exact mass calculated for $C_{18}H_{17}{}^{37}ClNO_3$ $[M+H]^+$, 332.0868. Found 332.0865 and exact mass calculated for $C_{18}H_{17}{}^{35}ClNO_3$ $[M+H]^+$, 330.0897. Found 330.0882. m/z (ES+) 332.0 {$[(C_{18}H_{17}{}^{37}ClNO_3)^+]$, 31%}, 330.0 {$[(C_{18}H_{17}{}^{35}ClNO_3)^+]$, 98%}, 125.0 (36%).

* Purified sample contains ~16 mol% of minor product assumed to be *trans* isomer by comparison with work by Charette in preparing *gem*-diacceptor cyclopropane **279**.[244]

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Chapter 3

Exploration of Asymmetric Induction by Rhodium(II) Carboxylates in the Transformations of α-Diazoacetates

Why do we fall down, sir? So we can learn to pick ourselves up.

Alfred Pennyworth, 'Batman Begins' (2005)

You find out that life is just a game of inches.
So is football.
Because in either game
life or football
the margin for error is so small.
I mean
one half step too late or to early
you don't quite make it.
One half second too slow or too fast
and you don't quite catch it.
The inches we need are everywhere around us.
They are in ever break of the game
every minute, every second.

On this team, we fight for that inch
On this team, we tear ourselves, and everyone around us
to pieces for that inch.
We claw with our finger nails for that inch.
Cause we know
when we add up all those inches
that's going to make the difference
between WINNING and LOSING.

Tony D'Amato, 'Any Given Sunday' (1999)

Contents

3.1 Introduction

The use of metal carbenoid complexes derived from transition metal catalysts has been widely investigated in a host of reaction pathways facilitating carbon–carbon bond formation and allowing preparation of structurally diverse substrates.[1-10] In 1981, Teyssié reported the first example of an intermolecular C–H insertion pathway using rhodium(II) acetate **1** with insertion into C–H bonds of alkanes.[11] This landmark discovery demonstrated the proficiency of rhodium(II) catalysts for α-diazocarbonyl transformations under milder conditions than required for copper(II)-mediated processes. The utility of rhodium(II) catalysts has been enhanced due to convenient ligand replacement of parent rhodium(II) acetate, allowing tuning of the reactivity and selectivity profiles of the catalyst. Variants of these prototypical complexes, **2**, **3**, **4** are among the most widespread catalysts for transition metal-catalysed transformations of α-diazocarbonyl compounds.[12]

In 1989, Brunner disclosed the synthesis of homochiral rhodium(II) carboxylate catalysts **5** for application in asymmetric synthesis (**Figure 3.1**), though only low enantioselectivitives (12% ee) were achieved using these catalysts.[13] Shortly thereafter, McKervey and Ikegami independently reported the preparation of chiral rhodium(II) carboxylates derived from proline[14] **6**, **7** and amino acids possessing the phthalimide backbone respectively (**Figure 3.2**).[15,16] In the early to mid-1990's, Davies and co-workers developed related proline-derived rhodium(II) carboxylate catalysts, Rh_2(*S*-TBSP)$_4$ **8** and Rh_2(*S*-DOSP)$_4$ **9**,[17-19] through the introduction of bulky *tert*-butyl and dodecyl substituents in the *para* position of the phenyl group, which also served to increase the solubility of the complexes. Additional substrate modifications by the same group involved design of conformationally rigid bridged derivatives **10** (**Figure 3.2**).[20] Like the general rhodium(II) acetate structure, the functionalised asymmetric rhodium(II) carboxylates consist of a dirhodium bridged cage within a 'lantern' structure with one vacant coordination site per metal atom. The electronic properties of the rhodium(II) carboxylates can be adjusted by the introduction of electron-withdrawing ligands on the metal centre,[21-28] leading to a more reactive and consequently less selective metallocarbenoid.

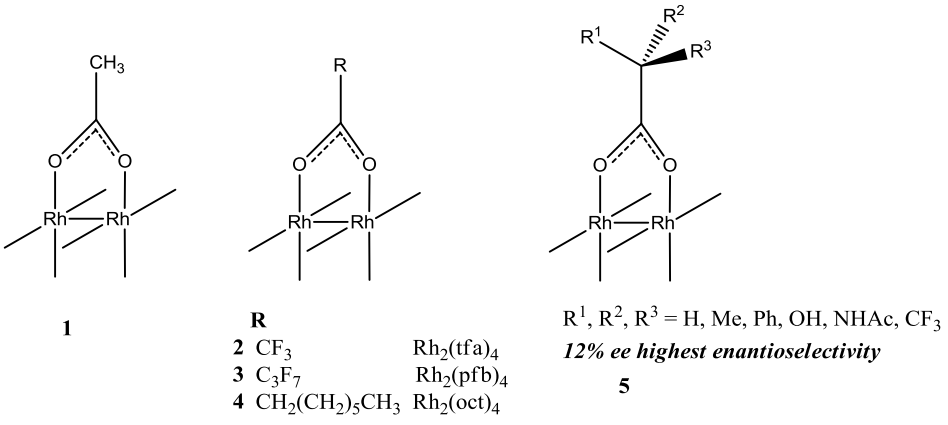
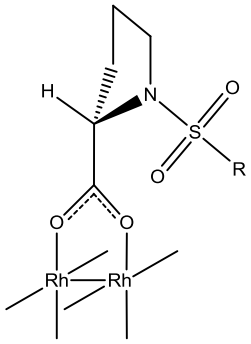
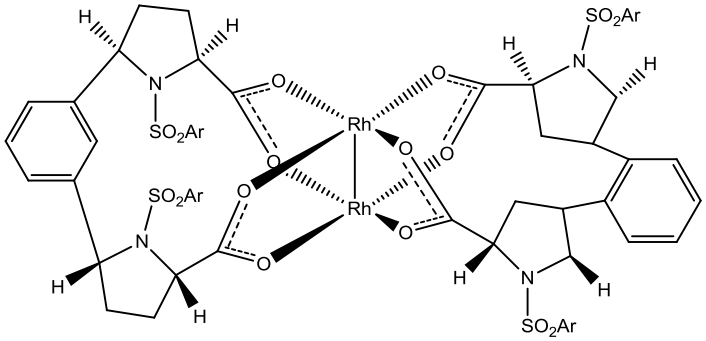


Figure 3.1 Achiral rhodium(II) carboxylates and homochiral rhodium(II) carboxylate catalysts developed by Brunner

Some of the more common asymmetric rhodium(II) carboxylates utilised in the field are shown below **11-25** (**Figure 3.2** and **Figure 3.3**). For rhodium(II) carboxylates, structural elaboration involves substituted proline, phthalimide or tetrahydroisoquinoline analogues attached to the chiral centre. The commercially available catalysts highlighted in red have been used in this project and will be discussed later (**Section 3.3**).

Proline-derived rhodium(II) carboxylates



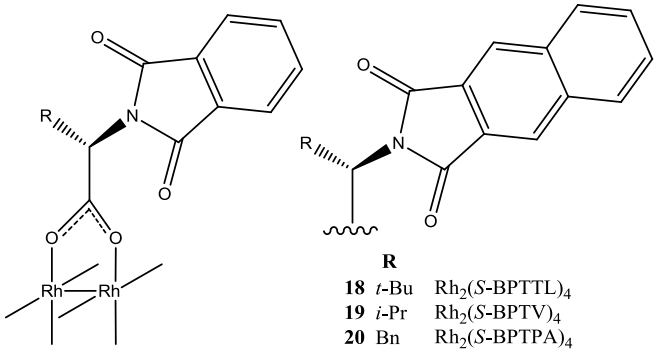


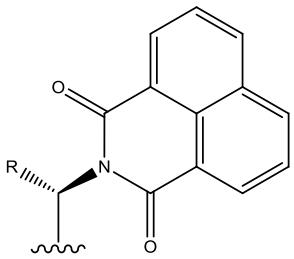
	R	
6	Ph	Rh_2(*S*-BSP)$_4$
7	2-naphthyl	Rh_2(*S*-NSP)$_4$
8	4-*t*-BuC_6H_4	Rh_2(*S*-TBSP)$_4$
9	4-($C_{12}H_{25}$)C_6H_5	Rh_2(*S*-DOSP)$_4$

	Ar	
10	2,4,6-tri-*i*-PrC_6H_4	Rh_2(*S*-biTISP)$_2$

Figure 3.2

Phthalimide and tetrahydroisoquinoline functionalised rhodium(II) carboxylates

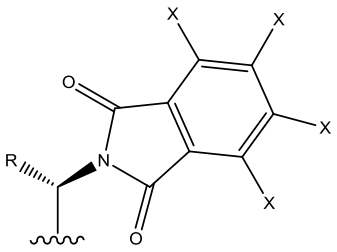




	R	
11	Me	Rh_2(*S*-PTA)$_4$
12	*i*-Pr	Rh_2(*S*-PTV)$_4$
13	*t*-Bu	Rh_2(*S*-PTTL)$_4$
14	Bn	Rh_2(*S*-PTPA)$_4$
15	Ph	Rh_2(*S*-PTPG)$_4$
16	$C(Et)_3$	Rh_2(*S*-PTTEA)$_4$
17	adamantyl	Rh_2(*S*-PTAD)$_4$

	R	
18	*t*-Bu	Rh_2(*S*-BPTTL)$_4$
19	*i*-Pr	Rh_2(*S*-BPTV)$_4$
20	Bn	Rh_2(*S*-BPTPA)$_4$
21	Me	Rh_2(*S*-BPTA)$_4$

	R	
22	*i*-Pr	Rh_2(*S*-NPV)$_4$
23	*t*-Bu	Rh_2(*S*-NPTL)$_4$

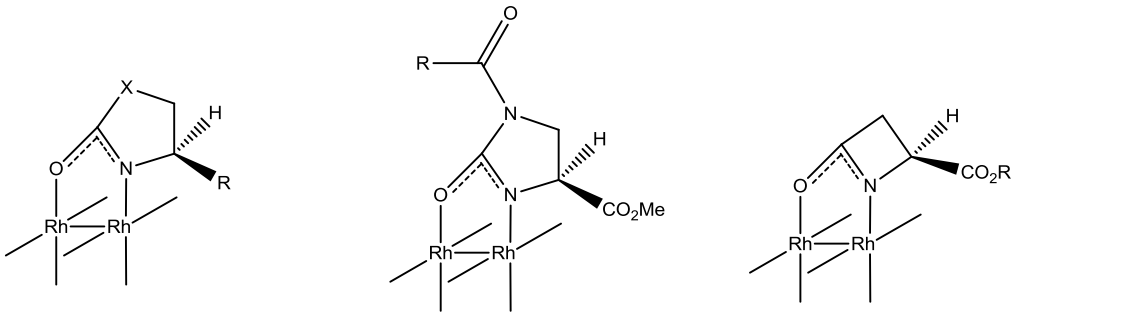


	R		
24	*t*-Bu	X = F	Rh_2(*S*-TFPTTL)$_4$
25	*t*-Bu	X = Cl	Rh_2(*S*-TCPTTL)$_4$

Figure 3.3

After extensive investigations into the introduction of carboxamidate ligands onto rhodium(II) acetate by Bear and co-workers in the early to mid-1980's,[29-31] Doyle established that tailoring of the ligands on the rhodium(II) catalyst can confer enantioselectivity in the transformations of diazo compounds.[12,32] The rhodium(II) carboxamidates have a characteristic assembly of four bridging ligands in a paddlewheel fashion possessing diaxial coordination sites adjacent to the rhodium atoms. A noteworthy point on the structural selectivity is that two oxygen and two nitrogen atoms are bonded to each rhodium atom, which due to coordination preferences are oriented in a *cis* configuration to each other (*cis*-2,2).[33] Structural diversification for the rhodium(II) carboxamidates **26-37** involves incorporation of proline, imidazoline, oxazolidine and azetidine derivatives into the bridgehead position of the ligand, as well as substitution on the heterocyclic component. This substrate architecture facilitates placement of the stereocentre in an adjacent position to the carbene carbon, which can result in further enhancement of enantioinduction (**Figure 3.4**).

Proline, oxazolidine, imidazoline and azetidine-derived rhodium(II) carboxamidates



	X	R	
26	CH_2	CO_2Me	Rh_2(5*S*-MEPY)$_4$
27	O	CO_2Me	Rh_2(5*S*-MEOX)$_4$
28	O	Bn	Rh_2(4*R*-BNOX)$_4$
29	O	Ph	Rh_2(4*R*-PHOX)$_4$

	R	
30	Me	Rh_2(4*S*-MACIM)$_4$
31	$Ph(CH_2)_2$	Rh_2(4*S*-MPPIM)$_4$
32	*c*-$C_6H_{11}CH_2$	Rh_2(4*S*-MCHIM)$_4$

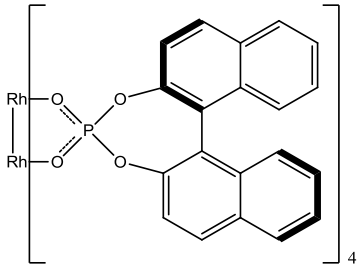
	R	
33	Me	Rh_2(4*S*-MEAZ)$_4$
34	*i*-Bu	Rh_2(4*S*-IBAZ)$_4$
35	Bn	Rh_2(4*S*-BNAZ)$_4$
36	*l*-menthyl	Rh_2(4*S*,*S*-MenthAZ)$_4$
37	*d*-menthyl	Rh_2(4*S*,*R*-MenthAZ)$_4$

Figure 3.4

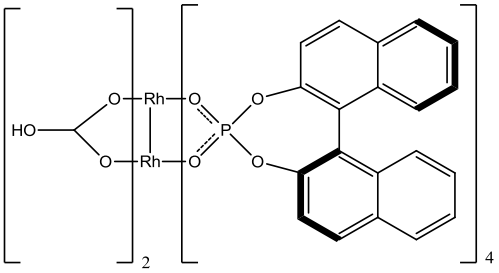
Alternative rhodium(II) catalyst templates include chiral phosphates developed by Pirrung,[34] Rh_2(*R*-BNP)$_4$ **38**, and McKervey,[35] Rh_2(*S*-BNP)$_2$(HCO_3)$_2$ **39** (**Figure 3.5**), while Capretta has generated achiral rhodium(II) phosphinates **40**, with a view to assembling related chiral catalysts (**Figure 3.5**).[36] A diverse range of *ortho*-metalated phosphine derivatives **41-43** have been prepared by Lahuerta[37] (**Figure 3.6**) and other ligand motifs such as thiocarboxylates **44**,[38] amidates **45**,[39] triazenides **46**,[40,41] anilinopyridines **47**[42-45] and 6-X-oxopyridines **48**[46,47] have also been utilised (**Figure 3.7**).

Chiral rhodium(II) phosphates

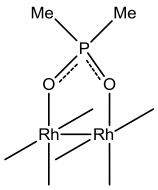
Achrial rhodium(II) phosphinate



38 Rh_2(*R*-BNP)$_4$



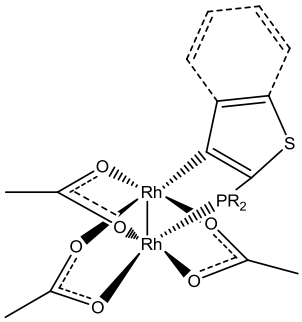
39 Rh_2(*S*-BNP)$_2$(HCO_3)$_2$



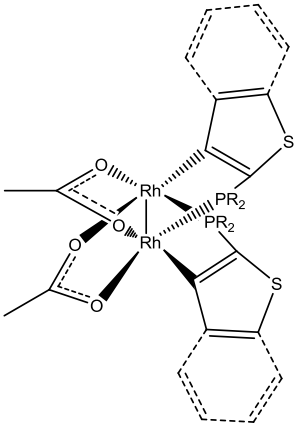
40 $Rh_2(O_2PMe_2)_4$

Figure 3.5

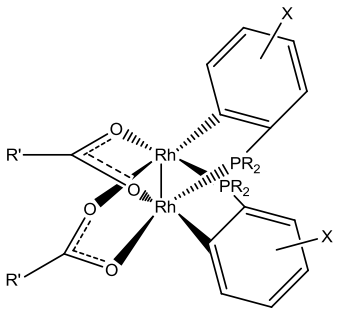
Ortho-*metalated phosphines*



41 R = 2-thienyl, 2-benzo[b]thienyl



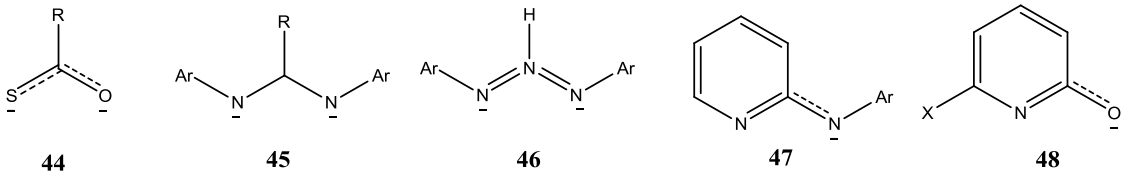
42 R = 2-thienyl, 2-benzo[b]thienyl



43 R = Aryl, R' =CF_3, Me, C_3F_7
Z = H, *p*-Me, CF_3, C_3F_7

Figure 3.6

Other ligand motifs



44 **45** **46** **47** **48**

Figure 3.7: Further bidentate ligand families

These catalysts have enabled rhodium(II)-catalysed transformations of α-diazocarbonyl compounds to develop in a highly enantio- and diastereoselective manner for a broad range of substrates, leading to a plethora of versatile synthetic intermediates.[1-10] Further targeted design of both bridged and axial ligands can allow tuning of the complex reactivity and selectivity, consolidating the position of rhodium(II) catalysis as a valuable method for asymmetric carbon–carbon bond forming reactions.

3.2 Objectives of applying chiral rhodium(II) catalysts in this project

The goals of this chapter can be summarised as follows;

- To synthesise known substrates applicable for inter- and intramolecular cyclopropanation and intramolecular C–H insertion reactions. Methods for determining enantioselectivity in their transformations using chiral stationary phase HPLC have been reported for the products **78** (*E*), **102**, **103**, **117** and **118**.

- To carry out a screening process using novel rhodium(II) catalysts with these substrates under mild conditions.

- To determine enantioselectivites using the novel catalysts; and to investigate the impact of steric and electronic variation of the catalyst on enantiopurities.

- To identify a catalyst which can deliver consistently high enantioselectivites across a range of substrates.

3.3 Investigation of asymmetric rhodium(II) catalysis in α-diazocarbonyl cyclisations

A novel series of rhodium(II) carboxylate catalysts were prepared in the Maguire group by Ford and contain various substituted mandelate ligands as well as tethering of monoterpenoid (–)-menthol and (+)-borneol auxiliaries to the general rhodium(II) mandelate template.[48] The series of catalysts allows investigation of the steric effects in the transformations studied. The three reaction pathways which were investigated in this work include intermolecular cyclopropanation, intramolecular cyclopropanation and intramolecular C–H insertion. The novel asymmetric rhodium(II) catalysts used in this work are shown below **49-61** (**Figure 3.8** and **Figure 3.9**).

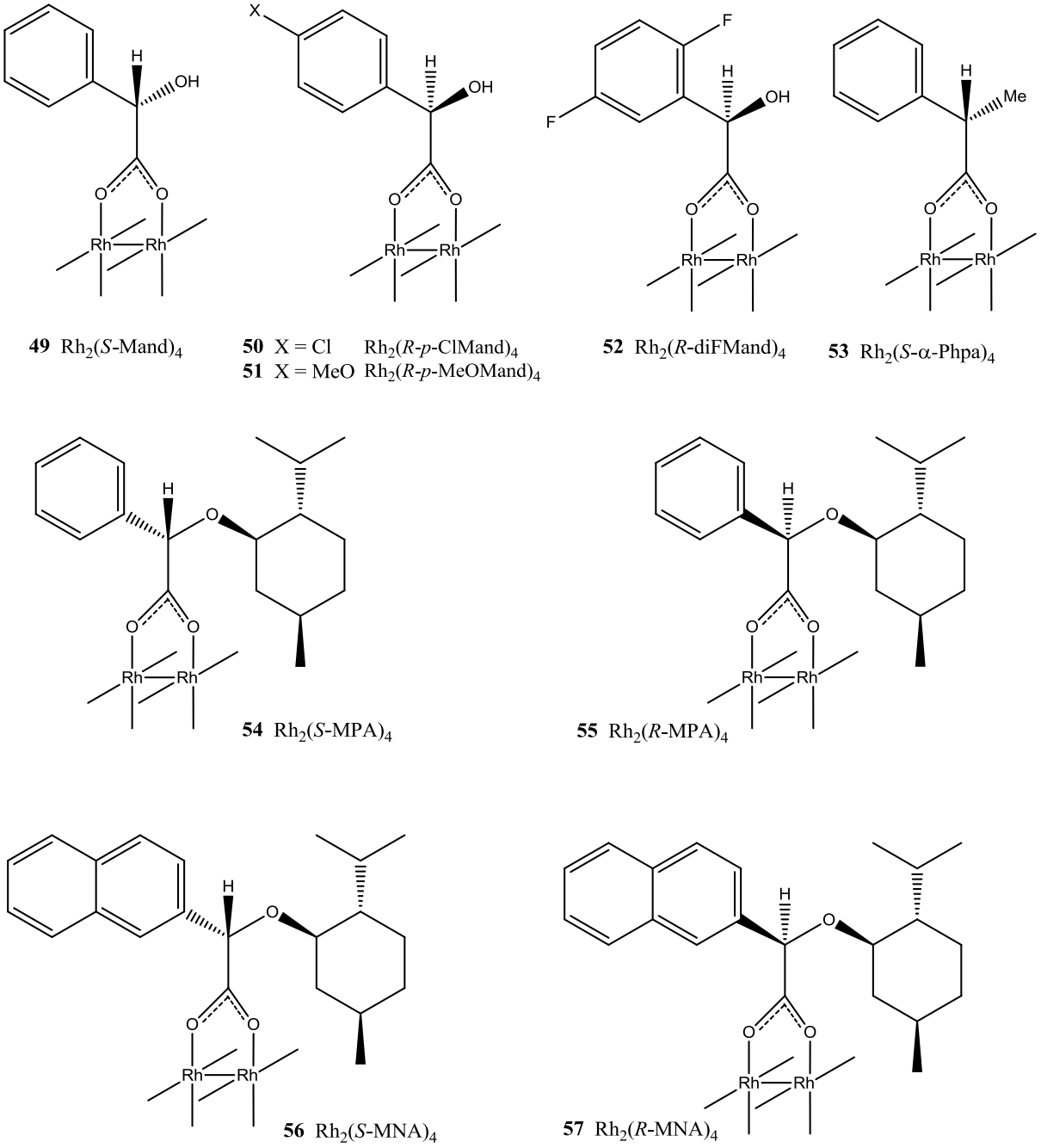


Figure 3.8: Chiral rhodium(II) catalysts used in this work[48]

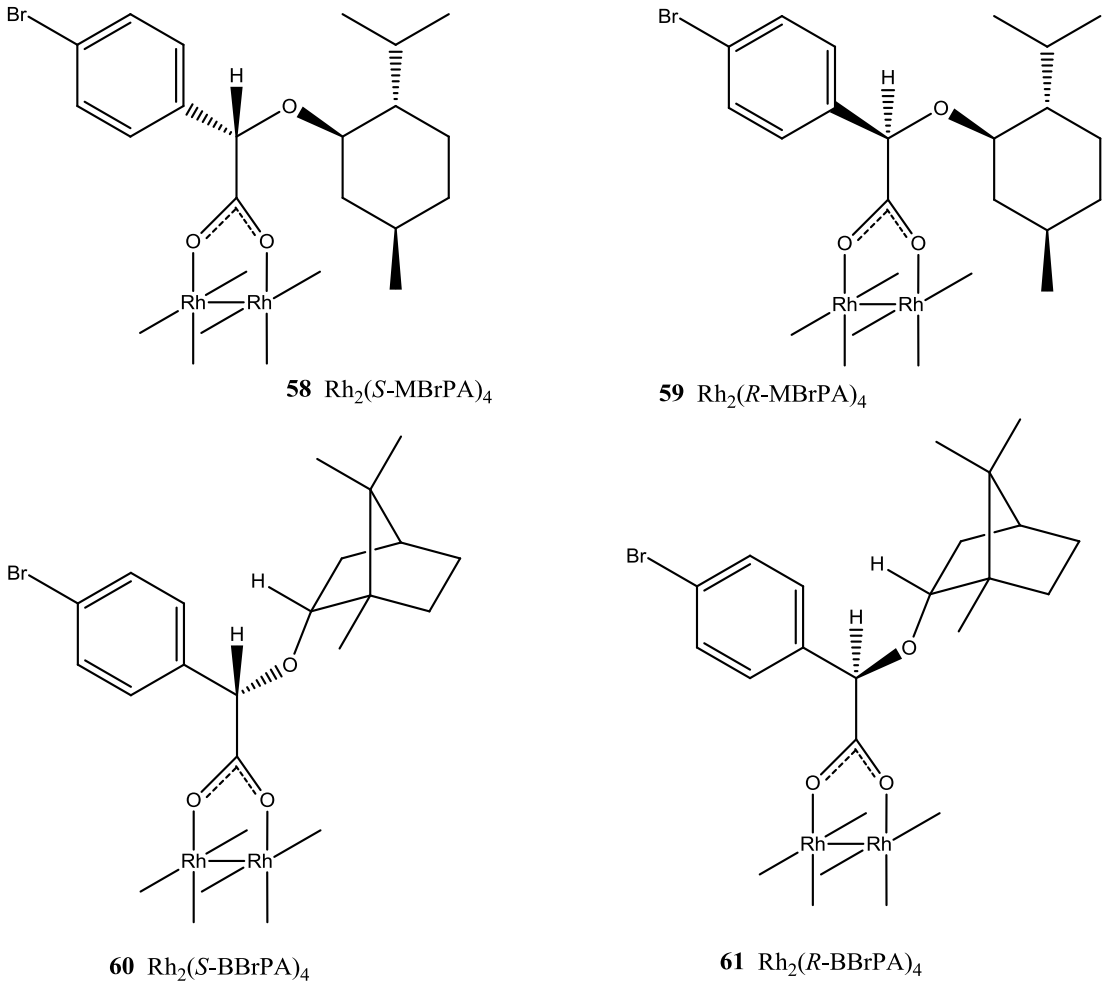
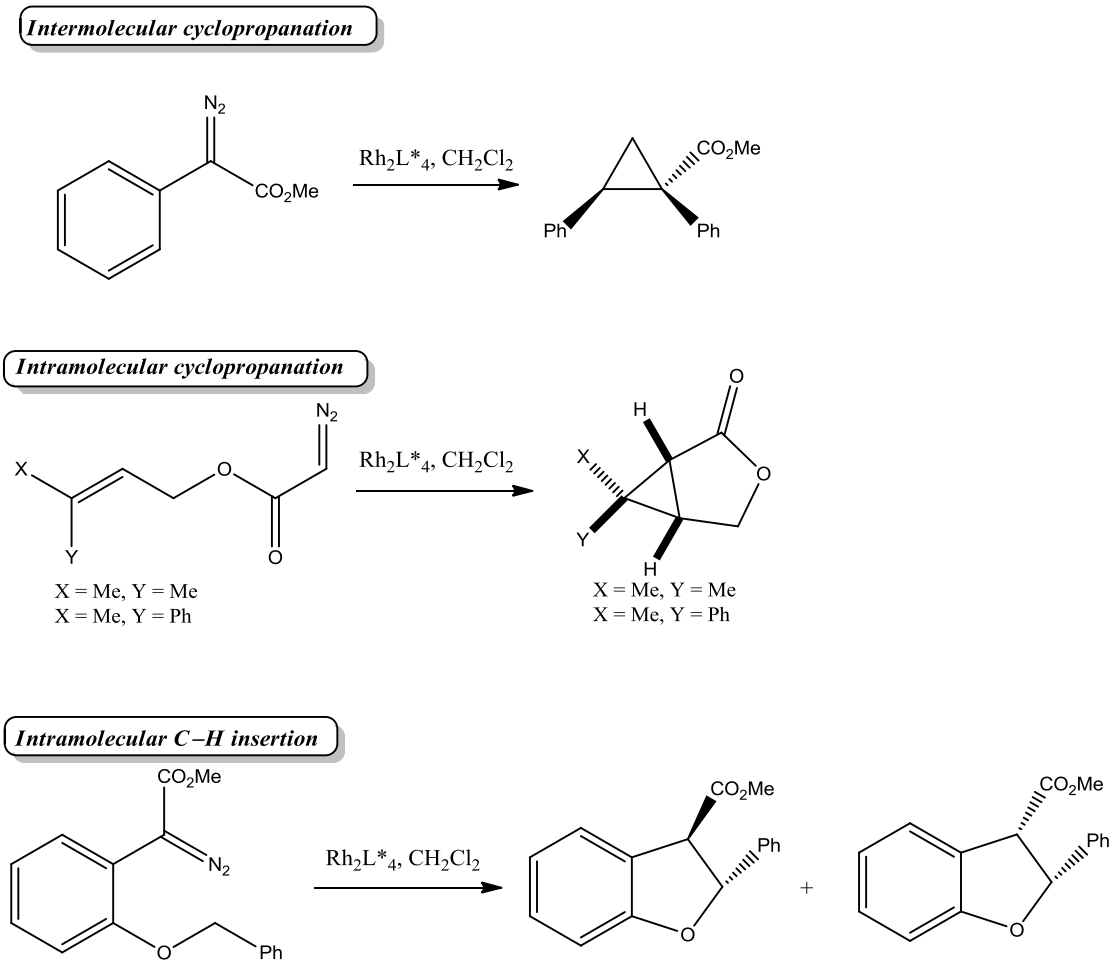


Figure 3.9: Chiral rhodium(II) catalysts used in this work[48]

An important aspect to consider is that in the preparation of the various chiral rhodium(II) catalysts by Ford,[48] it was not always possible to definitively assign an (*R*)- or (*S*)-configuration to the stereocentre at the benzylic carbon for the catalyst. Where this is the case, the less polar of the diastereomers purified by column chromatography was designed 'A', while the more polar diastereomer was designated 'B'. This designation was used for all the menthol- and borneol-derived catalysts used in this work.

The transition metal-catalysed transformations studied in this work involved intermolecular cyclopropanation, intramolecular cyclopropanation and intramolecular C–H insertion. The requisite α-diazoacetate precursors and the products obtained from these processes are shown below (**Scheme 3.1)**, in order to set out the synthetic strategy for this work.



Scheme 3.1

In the cases of the intermolecular cyclopropanation and intramolecular C–H insertion reactions, the metallocarbenoids generated from catalyst and α-diazoacetate fall under the heading of what Davies has classified as donor/acceptor carbenoids.[49] These systems impart a greater stability and selectivity for associated transformations compared to other metallocarbenoid systems (**Section 1.5.4.1**), which can be attributed to the ability of the donor group to modulate the reactivity of the carbenoid (**Figure 3.10**).[19,50,51] For the intramolecular cyclopropanations, the carbenoid from the allyldiazoacetates and catalyst are described as acceptor carbenoids, which are more reactive and less selective than the donor/acceptor carbenoids. The terms electron-withdrawing group (EWG) and electron-accepting group (EAG) are interchangeable but EWG will be preferentially used in this work.

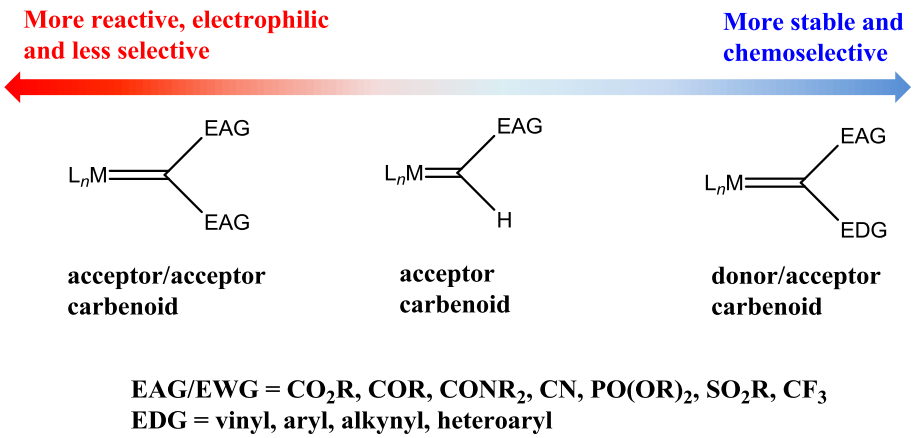


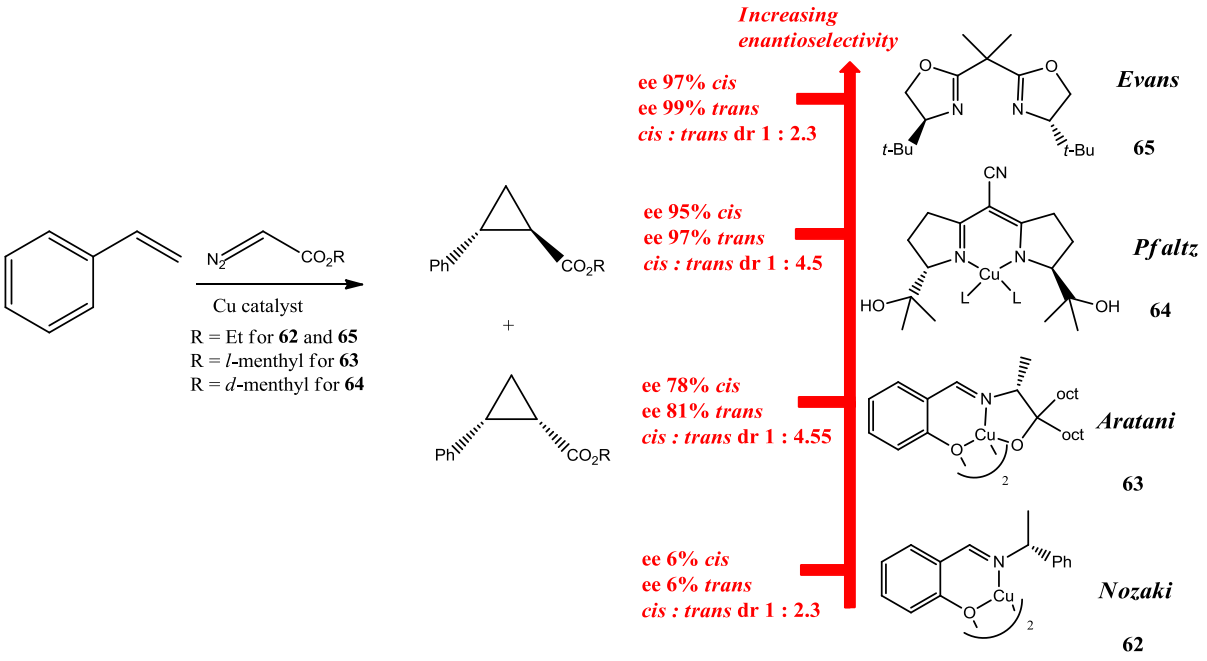
Figure 3.10: Davies' classification of metallocarbenoid systems and associated reactivity profiles

3.3.1 Intermolecular cyclopropanations

3.3.1.1 Background

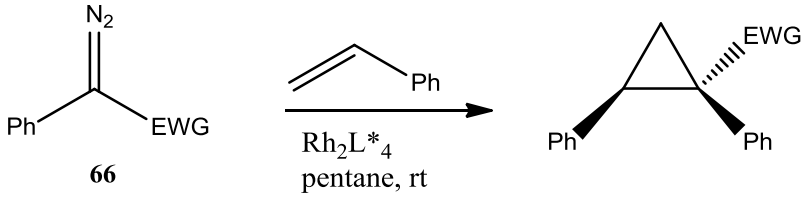
Following initial forays into intramolecular cyclopropanation by Stork and co-workers in the early 1960's,[52] the first successful reports of enantioinduction involving homogenous chiral transition metal complexes were disclosed in 1966 by Nozaki *et al.* in the intermolecular cyclopropanation of styrene using ethyl diazoacetate and a copper-Schiff base catalyst **62** (**Scheme 3.2**).[53] Isolation of the two diastereomers was achieved in a 1 : 2.3 diastereomeric ratio (*cis*/*trans*) with modest enantiopurities for *cis* (6% ee) and *trans* (6% ee) obtained. This seminal work was subsequently supplemented by efficient asymmetric intermolecular cyclopropanation of styrene employing copper-Schiff base ligands **63** developed by Aratani.[54-56] A favourable diastereomeric ratio of 1 : 4.55 was observed, as well as a substantial increase in enantioselectivity with 78% ee and 81% ee obtained for the *cis* and *trans* isomers respectively.

Further enhancement of enantioselectivity was accomplished by Pfaltz in the mid-1980's with a copper-semicorrin system **64**, *cis* (95% ee) and *trans* (97% ee), while also maintaining good diastereocontrol, dr 1 : 4.5 of *cis* : *trans* (**Scheme 3.2**).[57,58] The groups of Evans,[59] Masaumune[60] and Pfaltz[61] later independently prepared a range of asymmetric copper-ligand complexes possessing a bis(oxazoline) scaffold and ultimately demonstrated that high ee's could be obtained in the intermolecular cyclopropanation of styrene, albeit with only moderate diastereocontrol. Utilising the Evans bis(oxazoline) system **65** and Cu(OTf) as copper source, excellent enantioselectivities of 97% ee for the *cis* and 99% ee for the *trans* isomer were reported, along with an accompanying diastereomeric ratio of 1 : 2.3 (**Scheme 3.2**).[59] An interesting trend observed for the intermolecular cyclopropanation with α-diazoacetates is that the enantioselectivity is controlled by the use of appropriate catalyst, while the diastereomeric ratio is influenced by both the structure of the alkene[62] and the steric effect of the α-substituted ester group.[63]



Scheme 3.2

Some early work by Doyle[64] and Davies[19] (**Scheme 3.3**) demonstrated that high enantioselectivities could be obtained using donor/acceptor carbenoids **66**, with optimal results observed in nonpolar solvents *e.g.* pentane at ambient temperature (**Table 3.1**).

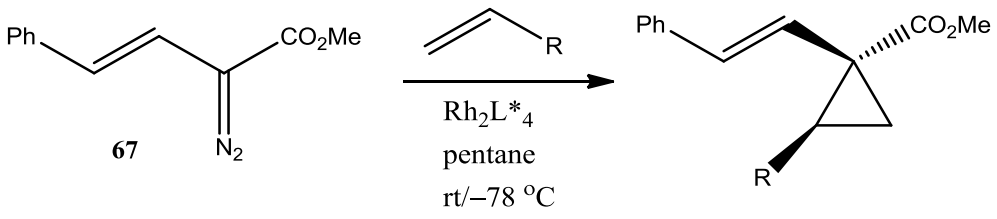


Scheme 3.3

Table 3.1

Entry	EWG	Catalyst	Yield (%)	ee (%)
1	CO_2Me	Rh_2(*S*-DOSP)$_4$ **9**	98	90
2	CO_2Me	Rh_2(*S*-biTISP)$_4$ **10**	72	89
3	$PO(OMe)_2$	Rh_2(*S*-DOSP)$_4$ **9**	69	34
4	$PO(OMe)_2$	Rh_2(*S*-biTISP)$_4$ **10**	89	88

Cyclopropanations of styrene by methyl styryldiazoacetate **67** have been examined by Davies using similar catalyst complexes to provide styrylcyclopropanes (**Scheme 3.4**).[18] Good yields and high enantioselectivities were obtained for the Rh_2(*S*-TBSP)$_4$ **8** and Rh_2(*S*-DOSP)$_4$ **9** catalysts specifically, with optimal results achieved in pentane at low temperatures (**Table 3.2**).

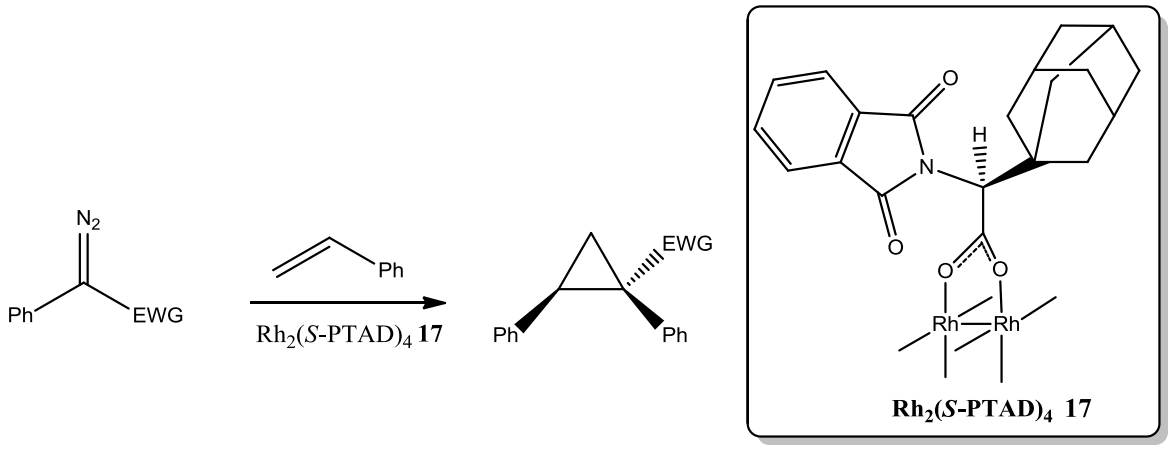


Scheme 3.4

Table 3.2

Entry	R	Catalyst/Temp.	Yield (%)	ee (%)
1	Ph	Rh_2(*S*-TBSP)$_4$ **8**/rt	79	90
2	Ph	Rh_2(*S*-DOSP)$_4$ **9**/–78 °C	68	98
3	Et	Rh_2(*S*-TBSP)$_4$ **8**/rt	65	>95

Optimisation of conditions by Davies has shown that asymmetric cyclopropanation of styrene by methyl phenyldiazoacetate (**Table 3.1**, entry 2) can proceed using very low loading of Rh_2(*S*-biTISP)$_4$ **10** catalyst (0.001 mol%) in high yields (76–91%) and high enantioselectivity (80–94% ee).[65] Davies *et al*. also employed polymer-supported versions of their Rh_2(*S*-biTISP)$_4$ and Rh_2(*S*-TBSP)$_4$ catalysts in the same process and the immobilised catalysts consistently generated high enantioselectivities in spite of low loading and repeated cycles, though associated with incrementally longer reaction times observed following repeated cycles.[66] Another aspect that can be modified is substitution of the methyl ester adjacent to the diazo moiety with other EWGs, thereby broadening the pool of substrates. Thus, further work by the same group has demonstrated that high enantiopurities could be achieved on compounds containing different α-substituents, namely α-substituted phosphonate,[67] trifluoromethyl,[68] nitrile[69] and acyl groups used in tandem with the phthaloyl adamantylglycine-derived Rh_2(*S*-PTAD)$_4$ catalyst **17** (**Scheme 3.5**).[70] This catalyst **17** was found to outperform the related Rh_2(*S*-PTTL)$_4$ **13** catalyst for these processes (**Table 3.3**).

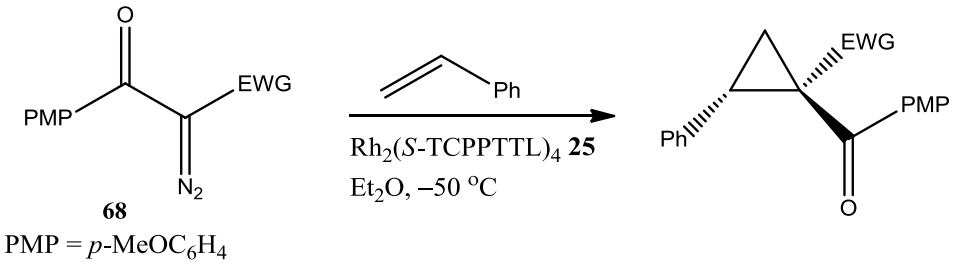


Scheme 3.5

Table 3.3

Entry	EWG	Conditions	Yield (%)	dr *E*/*Z*	*E*-isomer ee (%)
1	$PO(OMe)_2$	DMB, 50 °C	86	>30 : 1	99
2	CF_3	BTF, rt	94	>30 : 1	>98
3	CN	PhMe, –78 °C	86	>30 : 1	90
4	COMe	DMB, 50 °C	92	>95 : 5	85

Charette *et al*. have examined cyclopropanations of styrene using Rh_2(*S*-TCPTTL)$_4$ **25** as catalyst (**Scheme 3.6**) and a PMP (*para*-methoxyphenyl) substituted α-diazoketone **68** containing various EWGs (cyano, nitro and methyl ester) adjacent to the diazo moiety.[71] High enantio- and diastereomeric excess was achieved using this catalyst system (**Table 3.4**). The reactions were also carried out using a series of additives, though no improvement in diastereoselectivity or enantioselectivity was observed compared to the outcome in the absence of an additive.

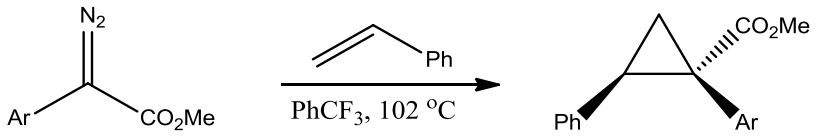


Scheme 3.6

Table 3.4

Entry	EWG	Conditions	Yield (%)	dr *E*/*Z*	ee (%)
1	NO_2	Et_2O, –50 °C, 16 h	81	98 : 2	99
2	CN	Et_2O, –35 °C, 16 h	98	95 : 5	84
3	CO_2Me	Et_2O, –40 °C, 16 h	60	99 : 1	88

Interestingly, Davies has recently disclosed cyclopropanation of styrene by aryldiazoacetates and aryldiazoketones in the absence of a transition metal catalyst, where the highly reactive free carbene is generated by thermolysis of the α-diazoacetate (**Scheme 3.7**).[72] This method is compatible with a range of aryl and heterocyclic α-diazoacetates and particularly in cases where the aryl group is electron-rich, cyclopropane products are obtained in high yields and high diastereoselectivity.

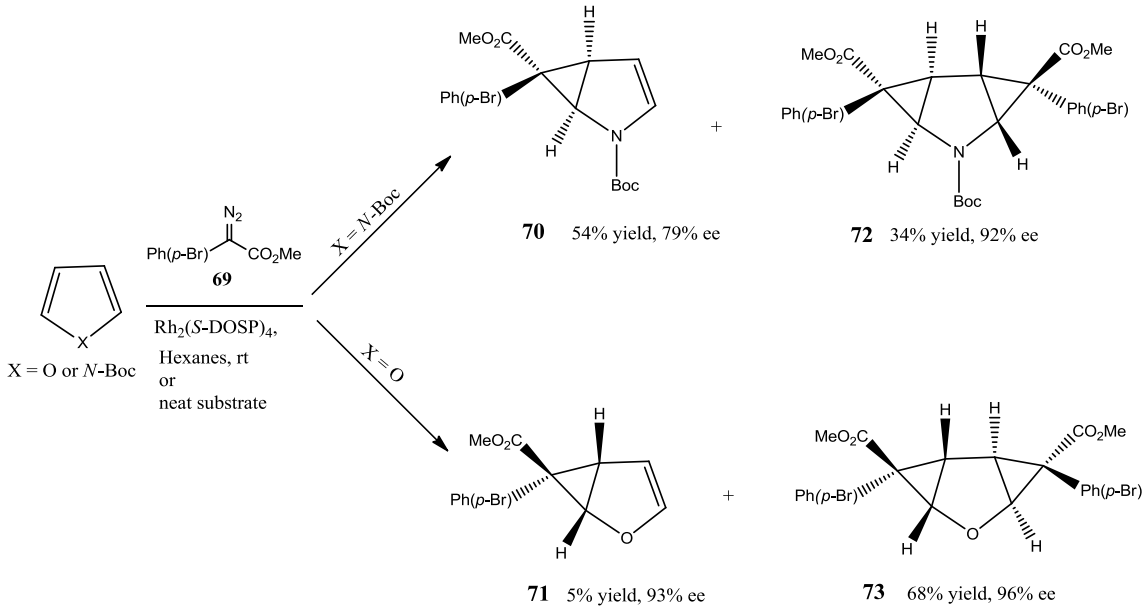


Ar = Ph, *p*-$MeOC_6H_4$
p-MeC_6H_4, *p*-BrC_6H_4

76–93% Yield
dr 79 : 21–95 : 5

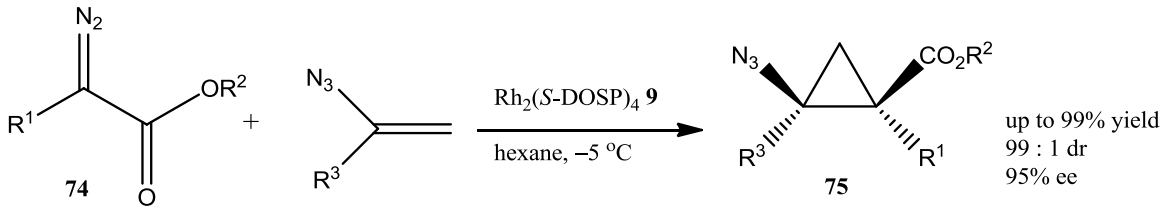
Scheme 3.7

Later investigations by the Davies group have centred on intermolecular cyclopropanations of electron-rich heterocycles with donor-acceptor carbenoids **69** (**Scheme 3.8**).[73,74] These heterocycles underwent either a single cyclopropanation to give **70** and **71** or a double cyclopropanation to provide **72** and **73**, which interestingly displayed the opposite sense of enantioinduction. The cyclopropanations of the *N*-Boc-protected pyrroles and furans proceeded in low to moderate yields and high enatioselectivities of up to 96% were obtained.



Scheme 3.8

More recently, further variation of the alkene moiety has been demonstrated by Gu in the enantioselective preparation of *cis*-β-azidocyclopropanes *via* intermolecular cyclopropanation (**Scheme 3.9**).[75] Reaction of azido alkenes with a range of structurally diverse α-diazoacetates **74**, in the presence of Rh_2(*S*-DOSP)$_4$ **9**, provided the cyclopropanes **75** incorporating an α-substituted azido group with the processes displaying excellent diastereo- and enantiocontrol.



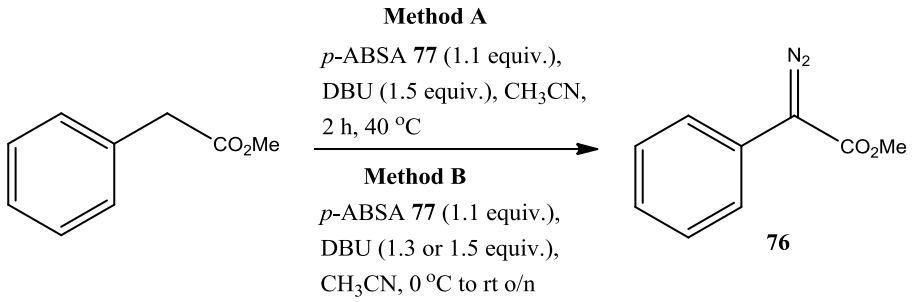
R^1 = Ph, *p*-$MeOC_6H_4$, *p*-BrC_6H_4, Naphth
R^2 = Et, Ph, Bn, *p*-MeOBn *p*-BrBn

R^3 = Ph, *p*-BrC_6H_4 *p*-$MeOC_6H_4$, *p*-FC_6H_4, *p*-CNC_6H_4, Naphth

Scheme 3.9

3.3.1.2 Formation of methyl phenyldiazoacetate 76

Following a general procedure outlined by Davies,[76] methyl phenyldiazoacetate **76** was prepared in one synthetic step from the commercially available starting material by diazo transfer using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) **77** and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**Scheme 3.10**). In a modification of Davies' procedure however, the reaction was carried out at 40 °C for 2 h *cf.* conditions of room temperature and stirred overnight in Davies' protocol.[76] This modified preparation was previously employed by Ford (Method A).[48] Completion of the reaction was determined by TLC and infrared spectroscopy, with additional portions of the *p*-ABSA (0.1 equiv.) added at 30 min intervals, if deemed necessary.



Scheme 3.10

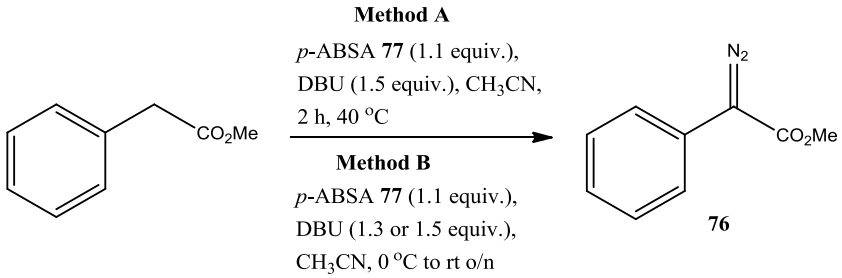
The ester starting material and methyl phenyldiazoacetate **76** were found to co-elute in the TLC analysis indicating the reaction did not go to completion but instead contained a mixture of both the starting material and the desired product (**Table 3.5**, entry 1). This was confirmed by infrared spectroscopy with a signal seen at ν_{max} 1741 cm^{-1}, corresponding to the methyl 2-phenylacetate starting material, as well as a stretch at ν_{max} 1706 cm^{-1} accounting for the presence of **76**. Purification by silica gel column chromatography provided the mixture of products (~29 mol% starting material and ~71 mol% α-diazoacetate **76**) in 67% mass recovery as a bright orange oil. Formation of α-diazoacetate **76** in the mixture was established by ^{1}H NMR spectroscopic analysis with the characteristic signal at δ_H 3.87 ppm, along with the appearance of two singlets at δ_H 3.63 ppm and 3.69 ppm, which are indicative of the starting material.

This impure product (~71 mol% **76** and 29% mol% starting material) was subsequently used as starting material for a repeat diazo transfer reaction following Davies' procedure (Method B),[76] while using the same molar ratios as employed for Method A. Analysis by TLC and infrared spectroscopy indicated completion of reaction and following chromatography, the purified methyl phenyldiazoacetate **76** was isolated in 93% mass recovery for the repeat reaction and in 53% overall yield based on starting material used for Method A (**Table 3.5**, entry 2) The spectral properties obtained were in excellent agreement with reported data.[77]

A further synthesis of methyl phenyldiazoacetate **76** from the commercial starting material employed Davies' procedure (Method B) using slightly modified molar ratios (1.3 equiv. *cf.* 1.2 equiv. DBU and 1.1 equiv. *cf.* 1.2 equiv. *p*-ABSA **77**). This procedure resulted in the formation of purified methyl phenyldiazoacetate **76** in a modest 66% isolated yield (**Table 3.5**, entry 3).

It should be noted that an alternative workup was employed during this work compared to the aqueous workup as described in the literature.[48] This departure consists of addition of silica gel (*ca.* 1 g/mmol ester) and removal of the acetonitrile *in vacuo*. Elimination of the solid residue is achieved by addition of (10:90) ethyl acetate/hexane, followed by vacuum filtration through Celite® and removal of the solvents under reduced pressure giving the crude α-diazoacetate as an orange oil. The purpose of this modified workup was to minimise the amount of the corresponding sulfonamide byproduct present, which Ford has found to ease the isolation of the α-diazoacetate after chromatography.[48] The method employed, mass recovery, isolated yield and overall yield obtained in this work are summarised below (**Table 3.5**).

Table 3.5



Entry	Procedure	Conditions	Mass Recovery (%)	Yield 76 (%)[b]
1	Method A	40 °C, 2h	67 (contains 71 : 29 mixture of **76** and starting material)	–
2	Method B using mixture of **76** and starting material from entry 1	rt, o/n	93 (based on mixture from entry 1)	53 overall yield based on starting material used for entry 1
3	Method B	rt, o/n	–	66

[a] Mass recovery of mixture after purification by column chromatography.
[b] Isolated yield of **76** after column chromatography.

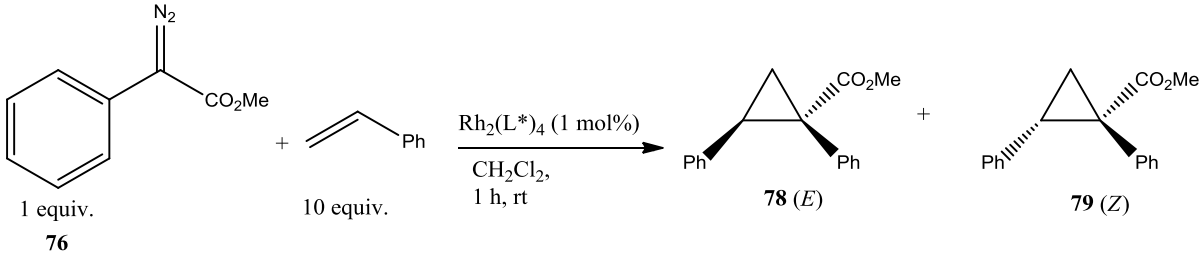
Thus, diazo transfer can be effected as described by Davies, at room temperature overnight.[76] However, Ford's procedure at elevated temperature and repeated additions of *p*-ABSA **77** enables a faster reaction but needs accurate monitoring of completion of the reaction.[48]

3.3.1.3 Synthesis of cyclopropanes using rhodium(II)-catalysed cyclisation

The next step involved screening of the intermolecular cyclopropanation of styrene by methyl phenyldiazoacetate **76** in the presence of a range of asymmetric rhodium(II) catalysts. Initial investigation employed the commercially available achiral $Rh_2(OAc)_4$ **1** and enantiopure Rh_2(*S*-DOSP)$_4$ **9** and Rh_2(*S*-PTTL)$_4$ **13** catalysts (**Scheme 3.11**). It was necessary to reproduce reported enantioselectivities on the standard catalysts before beginning the screening reactions with the novel rhodium(II) catalysts.

To ensure stringent elimination of oxygen, all the intermolecular cyclopropanations were carried out under Schlenk conditions (described in detail **Section 3.5**) with the freshly doubly distilled dichloromethane further degassed using the freeze, pump and thaw technique and all glassware was flame dried. A stirring solution of the catalyst (1 mol%), styrene (10 equiv.) and doubly distilled dichloromethane were placed under a nitrogen atmosphere at room temperature and a dichloromethane solution of methyl phenyldiazoacetate **76** was added slowly over 30 min by syringe pump. Completion of the reaction was determined by TLC and infrared spectroscopy, with formation of the cyclopropane usually observed within 1 h of completion of addition at room temperature. The infrared spectrum showed the disappearance

of the diazo stretching frequency at ν_{max} ~2098 cm^{-1}, as well as a shift of the carbonyl stretch from ν_{max} 1706 cm^{-1} in the α-diazoacetate **76** to ν_{max} 1717 cm^{-1} for the cyclopropane **78** (*E*).



Scheme 3.11

The crude reaction mixture contained a mixture of *trans* and the *cis* isomers, **78** (*E*) and **79** (*Z*), with the *E*-isomer **78** (*E*) predominating and diastereoselectivities of >97 : 3 normally observed. Doyle reported that the diastereomeric ratio was measured by integration of the methyl ester signals in the ^{1}H NMR of the crude reaction mixture.[64] The signal for the major isomer was located at δ_H 3.65 ppm, while the signal for the minor isomer was readily identifiable as a singlet at δ_H 3.32 ppm due to shielding of the methyl ester group by the adjacent phenyl ring.[78]

In purification of the cyclopropanes by column chromatography, it was essential to first flush the column with hexane to eliminate excess styrene in the crude reaction mixture. This prevents co-elution of styrene with cyclopropane product **78** (*E*). Once the styrene was eliminated, a new eluent system of ethyl acetate/hexane (5:95) was used with isolation of the purified cyclopropanes subsequently achieved. The cyclopropane was easily identified from the ^{1}H NMR spectrum, with distinctive doublets of doublets observed at δ_H 1.88 (*J* 7.6, 4.8 Hz), 2.13 (*J* 9.2, 4.8 Hz) and 3.11 (*J* 9.2, 7.6 Hz) ppm, which were consistent with literature values.[64,78] The ^{1}H NMR spectrum of purified cyclopropane **78** (*E*) is displayed below (**Figure 3.11**).

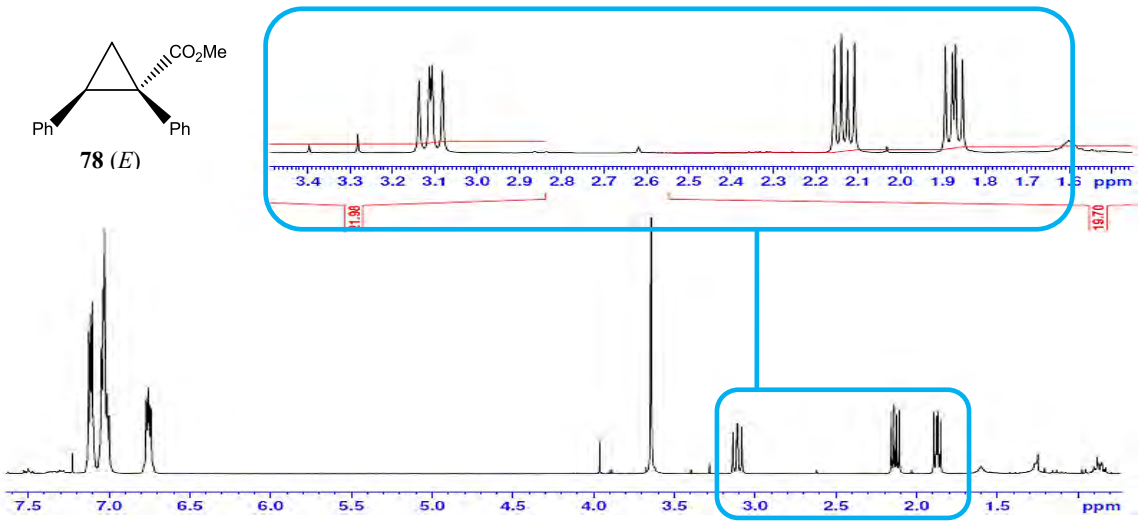


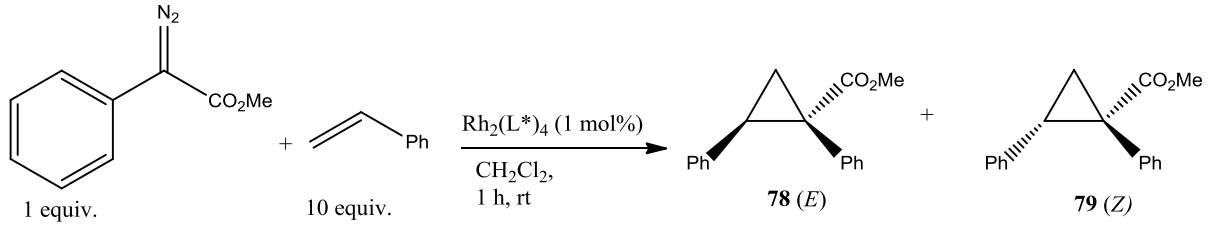
Figure 3.11: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 78 (*E*) with expansion of characteristic cyclopropane signals

On repeating cyclisations previously reported in the literature (**Table 3.6**), isolated yields of the cyclopropane **78** (*E*) were lower than expected for $Rh_2(OAc)_4$ **1** (69% *cf.* 37%, entry 1 *vs.* entry 2)[78], Rh_2(*S*-PTTL)$_4$ **13** (95 % *cf.* 43%, entry 6 *vs.* entry 7)[64] and Rh_2(*S*-DOSP)$_4$ **9** (69% *cf.* 40%, entry 4 *vs.* entry 5).[78] Doyle has reported that the major enantiomer isolated from HPLC analysis of the Rh_2(*S*-BSP)$_4$ **6** and Rh_2(*S*-TBSP)$_4$ **8**-catalysed cyclisations was the (1*R*,2*S*)-enantiomer, with the opposite (1*S*,2*R*)-enantiomer emerging as the favoured product in the case of the Rh_2(*S*-PTTL)$_4$ **13**-catalysed cyclisation.[64] Chiral HPLC analysis was undertaken with each sample of the cyclopropane **78** (*E*) following the conditions described by Bayardon,[79] employing Chiralpak OJ-H column (see *Appendix IV* for details). The enantiopurities obtained (**Table 3.6**, entries 5 and 7) were comparable both in scale and direction to the literature results using the known catalysts (**Table 3.6**, entries 4 and 6).[64,78] Having established reproducibility with literature data,[64,78] the next step involved carrying out intermolecular cyclopropanations using the novel asymmetric rhodium(II) catalysts.

The intermolecular cyclopropanation reactions employing Ford's novel rhodium(II) catalysts were carried out using the same general procedure, with the isolated yields of the cyclopropane **78** (*E*) varying from 41% yield for the Rh_2(*R*-*p*-MeOMand)$_4$ **51** catalyst to an impressive 92% yield for the Rh_2(*R*-diFMand)$_4$ **52** catalyst. High diastereomeric ratios of typically >97 : 3 were observed in all cases and the overall results are summarised below (**Table 3.6**).

Chiral HPLC analysis of the cyclopropanes was carried out under conditions as outlined in *Appendix IV* following a literature method from Bayardon.[79] This resulted in good separation of enantiomers in all of the examples, though the ee's from these cyclisations only ranged from negligible to moderate with the highest enantiopurities of 18% ee observed for the Rh_2(*S*-α-PhPa)$_4$ **53**, Rh_2('A'-MPA)$_4$ **54/55**, and Rh_2('A'-BBrPA)$_4$ **60/61** catalysts (**Table 3.6**, entries 11, 12 and 17), with the latter catalyst conferring the opposite enantioinduction to both of the former catalysts {(1*R*,2*S*) *cf.* (1*S*,2*R*)}. Other catalysts which displayed some degree of asymmetric induction included Rh_2(*R*-*p*-MeOMand)$_4$ **51**, and Rh_2('B'-MBrPA)$_4$ **58/59** (**Table 3.6**, entries 8 and 16). Overall, values obtained in this work were much lower than achieved by Davies using Rh_2(*S*-DOSP)$_4$ **9** (**Table 3.6**, entry 4),[78] which appears to be a very suitable catalyst for this particular transformation. A summary graph of the enantioselectivities is displayed below (**Figure 3.12**).

Table 3.6 *Rhodium(II)-catalysed intermolecular cyclopropanations of* **78** (*E*)[a]



Entry	Catalyst	Time (h)	Solvent	78 (*E*) : 79 (*Z*)[b]	Yield78 (*E*) (%)[c]	ee of 78 (*E*) (%)[d,e]
1	$Rh_2(OAc)_4$ **1**	1.0	DCM	98 : 2	69	–[78]
2	$Rh_2(OAc)_4$ **1**	1.0	DCM	99 : 1	37	~0[f]
3	Rh_2(*S*-BSP)$_4$ **6**	1.0	DCM	97 : 3	45	60 (1*R*,2*S*)[64]
4	Rh_2(*S*-DOSP)$_4$ **9**	1.0	DCM	98 : 2	69	69 (1*R*,2*S*)[78]
5	Rh_2(*S*-DOSP)$_4$ **9**	1.0	DCM	–	40	69 (1*R*,2*S*)
6	Rh_2(*S*-PTTL)$_4$ **13**	1.0	DCM	98 : 2	95	34 (1*S*,2*R*)[64]
7	Rh_2(*S*-PTTL)$_4$ **13**	1.0	DCM	–	43	21 (1*S*,2*R*)
8	Rh_2(*R*-*p*-MeOMand)$_4$ **51**	1.0	DCM	98 : 2	41	16 (1*R*,2*S*)
9	Rh_2(*R*-*p*-ClMand)$_4$ **50**	1.0	DCM	98 : 2	44	~0[f]
10	Rh_2(*R*-diFMand)$_4$ **52**	1.0	DCM	98 : 2	92	~0[f]
11	Rh_2(*S*-α-Phpa)$_4$ **53**	1.0	DCM	>99 : 1	59	18 (1*S*,2*R*)
12	Rh_2('A'-MPA)$_4$ **54/55**	1.0	DCM	99 : 1	49	18 (1*S*,2*R*)
13	Rh_2('B'-MPA)$_4$ **54/55**	1.0	DCM	99 : 1	76	9 (1*S*,2*R*)
14	Rh_2('A'-MNA)$_4$ **56/57**	1.0	DCM	98 : 2	65	8 (1*R*,2*S*)
15	Rh_2('B'-MNA)$_4$ **56/57**	1.0	DCM	98 : 2	71	~0[f]
16	Rh_2('B'-MBrPA)$_4$ **58/59**	1.0	DCM	97 : 3	43	15 (1*S*,2*R*)
17	Rh_2('A'-BBrPA)$_4$ **60/61**	1.0	DCM	99 : 1	53	18 (1*R*,2*S*)

[a] Reactions conducted using the general procedure for rhodium-catalysed intermolecular cyclopropanation reactions.
[b] Ratios based on integration of the methyl ester ($CO_2C\underline{H}_3$) signals from the ^{1}H NMR spectra of the crude products.[78]
[c] Yield of **78** (*E*) following column chromatography.
[d] Determined by chiral stationary phase HPLC on material **78** (*E*) after chromatography (see *Appendix IV* for details).
[e] Entries 1, 3, 4, 6 refer to literature data.[64,78] Assignment of stereochemistry of the products is by comparison with previously reported data.[64,78]
[f] Where enantiomeric excess was ≤ 5% the sample was regarded as achiral.

Comparison of enantioselectivities for **78** (*E*) *from rhodium(II)-catalysed intermolecular cyclopropanation of α-diazoacetate* **76**

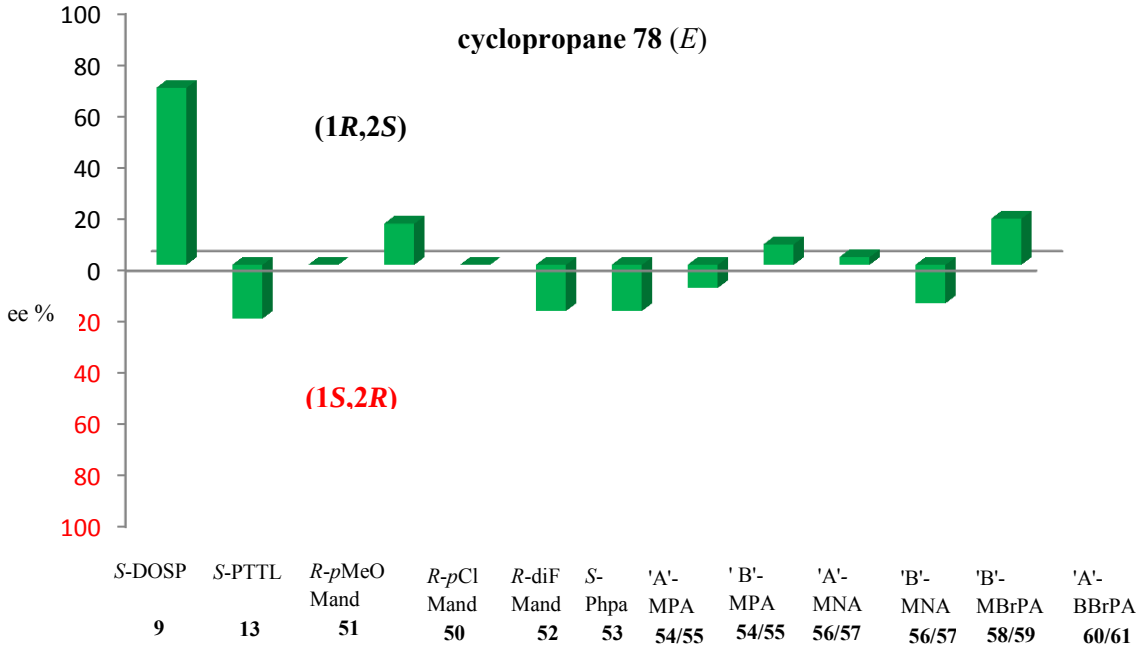
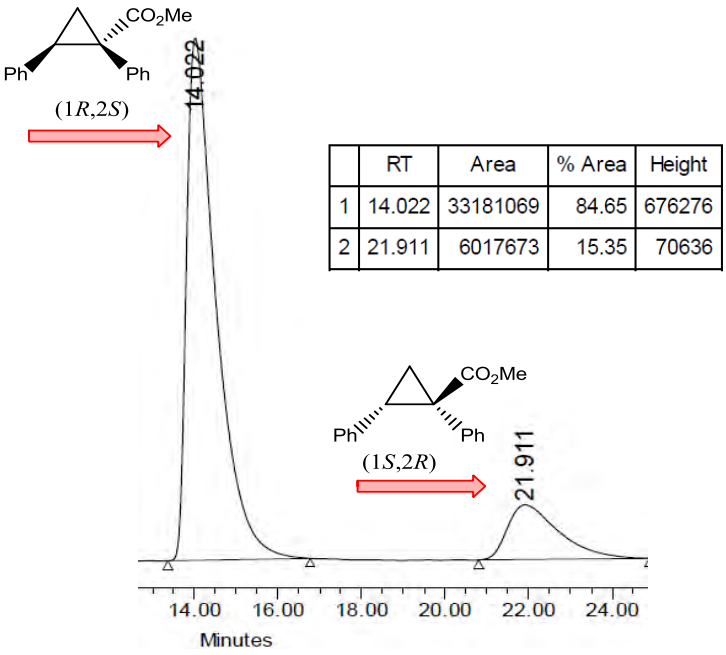


Figure 3.12

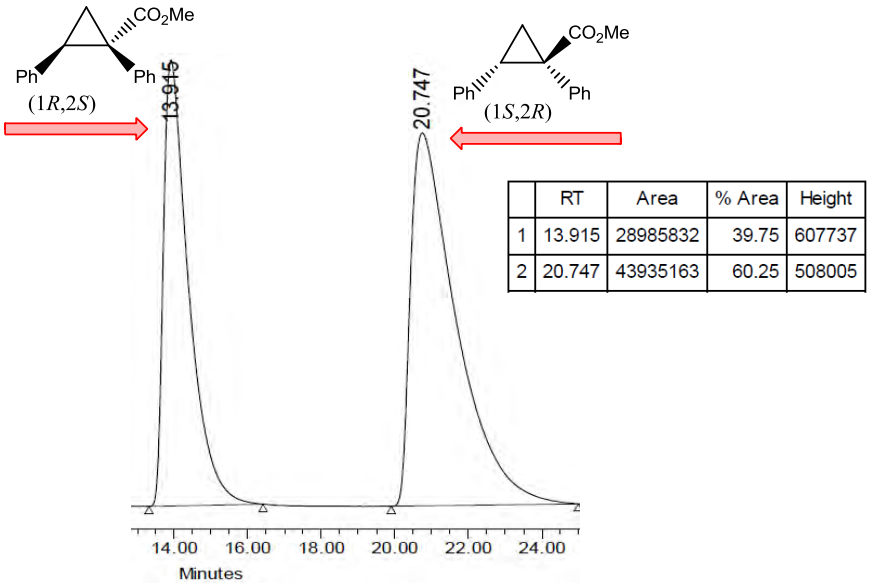
The HPLC traces are shown in **Figure 3.13–3.16**, with the notable switching of enantiomeric excess observed between Rh_2(*S*-Phpa)$_4$ **53**, (1*S*,2*R*) and Rh_2('A'-BBrPA)$_4$ **60/61**, (1*R*,2*S*).

An interesting observation was that HPLC conditions showed a degree of variability in the retention times possibly due to variation in the column over time. For cyclopropane product **78** (*E*) formed from the commercial Rh_2(*S*-DOSP)$_4$ **9** and Rh_2(*S*-PTTL)$_4$ **13** catalysts, retention times of 13.9 min and 20.5 min differed to retention times of 16.0 min and 26.2 min obtained for Ford's novel rhodium(II) catalysts. Following this, a mixed injection confirmed that the same materials were present from the reactions using cyclopropane **78** (*E*) formed from reactions using Rh_2(*S*-DOSP)$_4$ **9** and Rh_2('A'-BBrPA)$_4$ **60/61** (**Table 3.6**, entries 5 and 17). While Bardayon previously reported chiral HPLC conditions for substrate **78** (*E*), surprisingly no retention times were provided in that work.[79] The author stated that confirmation of enantiomers was determined by comparison with retention times of authentic samples.



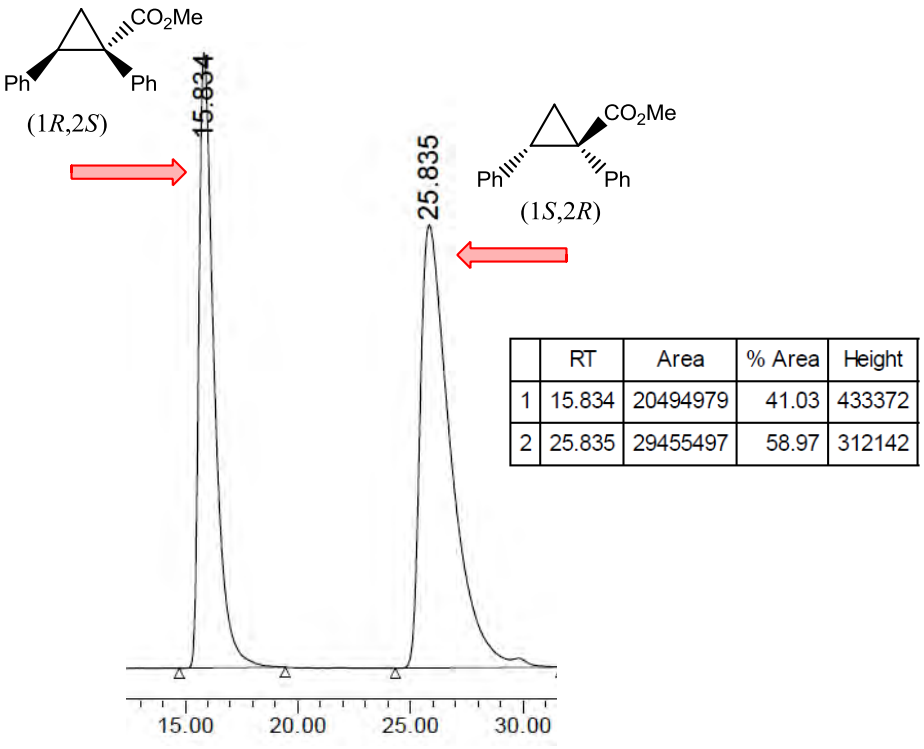
	RT	Area	% Area	Height
1	14.022	33181069	84.65	676276
2	21.911	6017673	15.35	70636

Figure 3.13: Rh_2(*S*-DOSP)$_4$-catalysed intermolecular cyclopropanation of 76 (Table 3.6, entry 4) (69% ee)



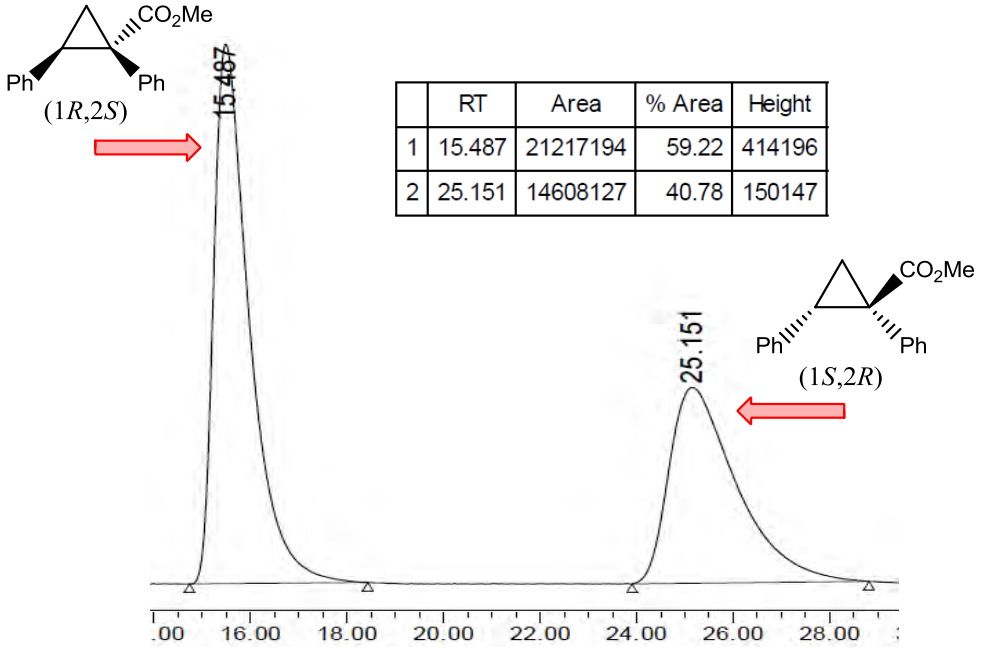
	RT	Area	% Area	Height
1	13.915	28985832	39.75	607737
2	20.747	43935163	60.25	508005

Figure 3.14: Rh_2(*S*-PTTL)$_4$-catalysed intermolecular cyclopropanation of 76 (Table 3.6, entry 6) (21% ee)



	RT	Area	% Area	Height
1	15.834	20494979	41.03	433372
2	25.835	29455497	58.97	312142

Figure 3.15: Rh_2(*S*-α-Phpa)$_4$-catalysed intermolecular cyclopropanation of 76 (Table 3.6, entry 11) (18% ee)



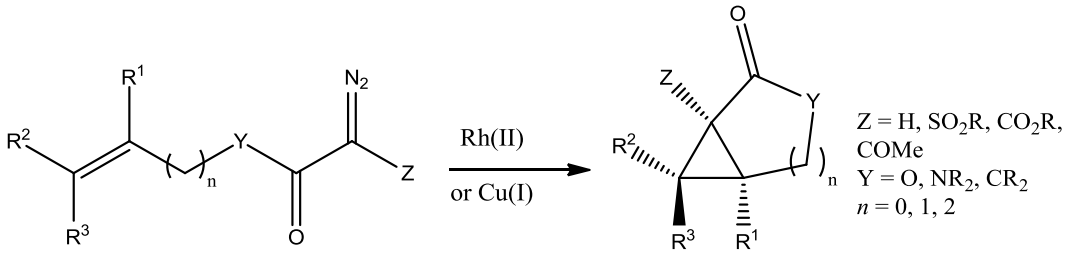
	RT	Area	% Area	Height
1	15.487	21217194	59.22	414196
2	25.151	14608127	40.78	150147

Figure 3.16: Rh_2('A'-BBrPA)$_4$-catalysed intermolecular cyclopropanation of 76 (Table 3.6, entry 17) (18% ee)

3.3.2 Intramolecular cyclopropanation

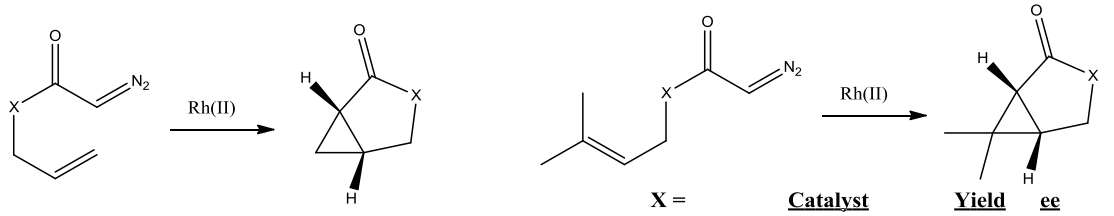
3.3.2.1 Background

In 1961, Stork and Ficini reported the first example of an intramolecular cyclopropanation using transition metal catalysis.[52] This has served as the template for this methodology which has since been extensively investigated.[32,80-82] This strategy has found widespread use in the synthesis of bicyclic lactones and lactams arising from cyclisation of the corresponding α-diazoacetates and α-diazoacetamides (**Scheme 3.12**). The various chiral rhodium(II) carboxamidate catalysts (**Figure 3.3**) developed by Doyle are among the most efficient and prevalent catalysts for this transformation as these catalysts have permitted high enantiopurities to be obtained for this process.



Scheme 3.12

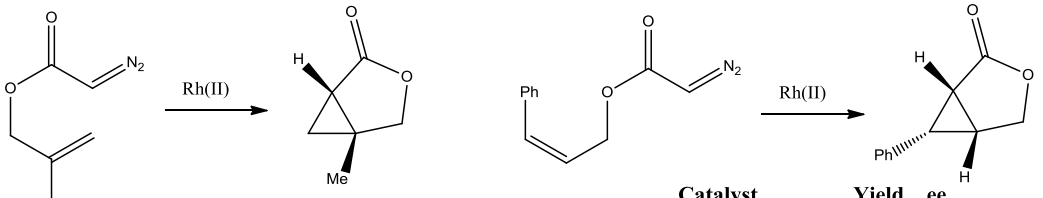
The α-diazoacetates and α-diazoacetamides of this type exhibit a propensity to form fused 5-membered lactones and lactams upon cyclisation in the presence of a transition metal catalyst,[82] although larger ring sizes involving fused 6-membered cyclopropyl lactone systems have also been prepared.[81] A key aspect of this transformation is the generation of 3-oxabicyclo[3.1.0]hexan-2-one and 3-azabicyclo[3.1.0]hexan-2-one derivatives bearing three contiguous stereocentres in one synthetic operation, with the formation of only one diastereomer in the process.[9] Doyle and co-workers have achieved high to excellent enantioselectivities using rhodium(II) carboxamidate catalysts on a series of substituted α-diazoacetates and α-diazoacetamides and these bicyclic compounds can serve as valuable intermediates for stereoselective synthesis (**Schemes 3.13**–**3.15**).[32,81]



X=	Catalyst	Yield	ee
O	Rh_2(5*S*-MEPY)$_4$	75%	7%
O	polymer bound	81%	95%
O	Rh_2(4*S*-MEOX)$_4$	95%	94%
O	Rh_2(4*S*-IBAZ)$_4$	92%	80%
NH	Rh_2(4*S*-MEOX)$_4$	40%	98%
NMe	Rh_2(4*S*-MEOX)$_4$	45%	86%
NMe	Rh_2(4S-MEPY)$_4$	62%	93%

X =	Catalyst	Yield	ee
O	Rh_2(5*S*-MEPY)$_4$	89%	98%
NMe	Rh_2(4S-MEOX)$_4$	91%	94%
NMe	Rh_2(4*S*-BNAZ)$_4$	88%	94%

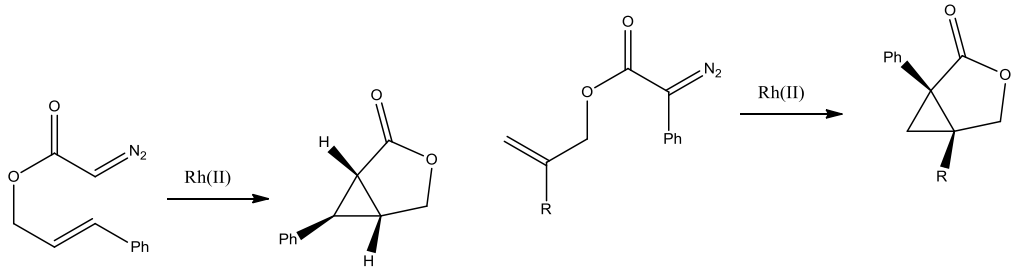
Scheme 3.13



Catalyst	Yield	ee
Rh_2(5*S*-MEPY)$_4$	75%	7%
Rh_2(4*S*-MPPIM)$_4$	61%	89%

Catalyst	Yield	ee
Rh_2(5*S*-MEPY)$_4$	70%	94%

Scheme 3.14: Bicyclic lactones and lactams (Scheme adapted from Ford)[63]

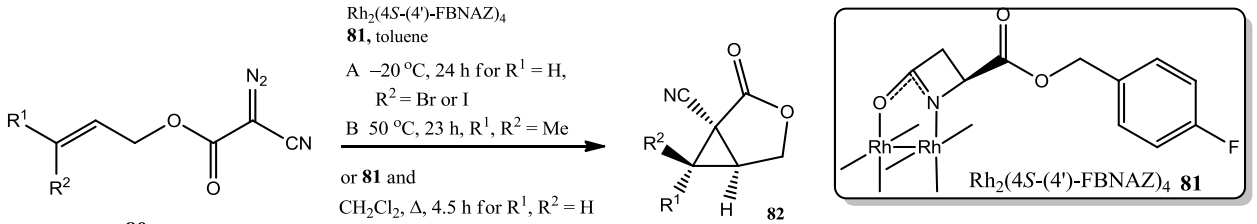


Catalyst	Yield	ee
Rh_2(5*S*-MEPY)$_4$	75%	7%
Rh_2(4*S*-MPPIM)$_4$	61%	89%

R	Catalyst	Yield	ee
H	Rh_2(5*S*-MEAZ)$_4$	80%	68%
H	Rh_2(4*S*-IBAZ)$_4$	83%	64%
Me	Rh_2(5*S*-MEAZ)$_4$	82%	84%
Me	polymer bound	80%	88%
Me	Rh_2(4*S*-BNAZ)$_4$	80%	83%

Scheme 3.15: Bicyclic lactones (Scheme from Ford)[63]

Charette has described the asymmetric intramolecular cyclopropanation of 3-substituted-2-propenyl cyanodiazoacetates **80**, applying a novel rhodium catalyst, Rh_2[4S-(4')-FBNAZ]$_4$ **81** (**Scheme 3.16**).[83] The bicyclic lactones **82** were successfully generated with enantioselectivity of up to 91% ee achieved. Enantioinduction in the reaction appeared to be dependent upon the nature of the substituents on the alkene portion of the substrate. This was evident with the bromine and iodine substituted α-cyanodiazoacetates cleanly forming the corresponding cyclopropanes in moderate yield and high enantiopurity, in contrast to the alkyl substituted cyanodiazoacetates which gave varied enantiopurities. The optimal reaction conditions involved a reaction temperature of –20 °C with toluene as solvent and reaction carried out over 24 h.



80

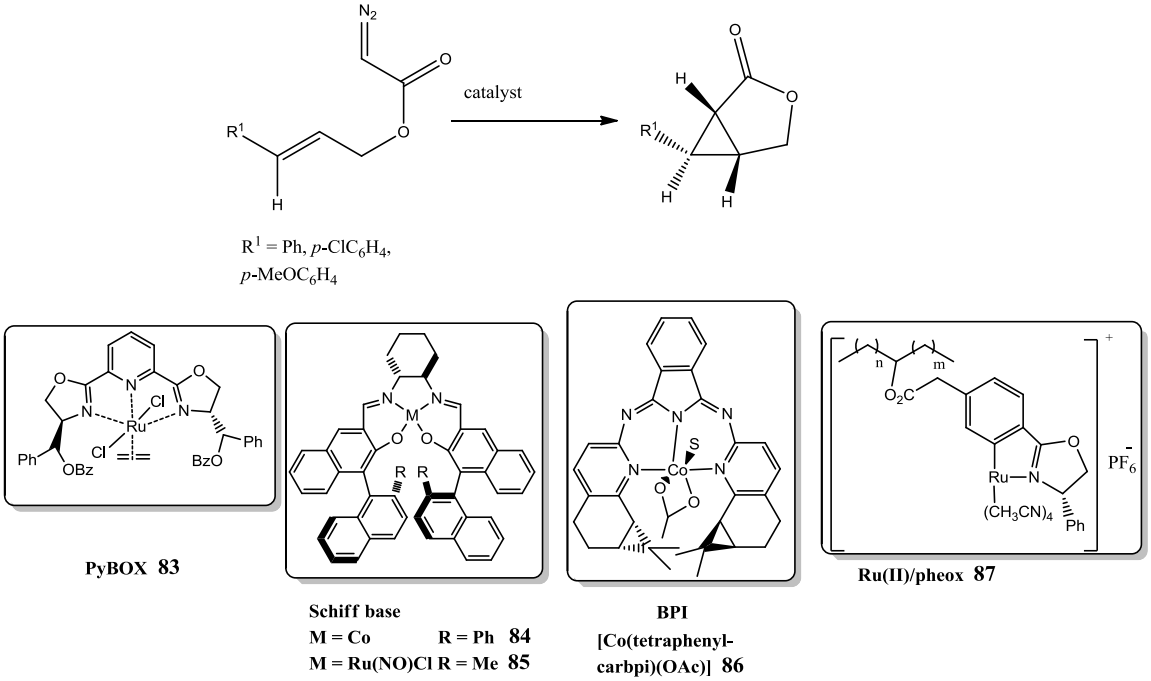
R^1 = H, Me, Ph
R^2 = H, Me, Br, I

82

R^1, R^2 = H 85% yield, 85% ee
R^1, R^2 = Me 37% yield, 56% ee
R^1 = Ph, R^2 = H 35% yield, 29% ee
R^1 = H, R^2 = Br 57% yield, 91% ee
R^1 = H, R^2 = I, 55% yield, 86% ee

Scheme 3.16

Traditionally, rhodium(II) and copper catalysts have dominated the landscape for asymmetric intramolecular cyclopropanations, but some excellent results have also been obtained through the use of ruthenium and cobalt catalysts encompassing a wide variety of ligands including porphyrin[84] and novel PyBOX ligands[85] **83** (**Scheme 3.17**). It was noted by Katsuki and co-workers that cobalt(II)-Schiff base complexes **84** outperformed their ruthenium counterparts **85** in these reactions.[86,87] Some interesting variants of the ligands include the use of *bis*(pyridylimino)isoindoles (BPI) **86** as stereodirecting units in these cyclisations,[88] with a novel macroporous polymer-supported ruthenium(II)/phenyloxazoline (Ru^{II}/pheox) complex **87** also utilised to good effect.[89]

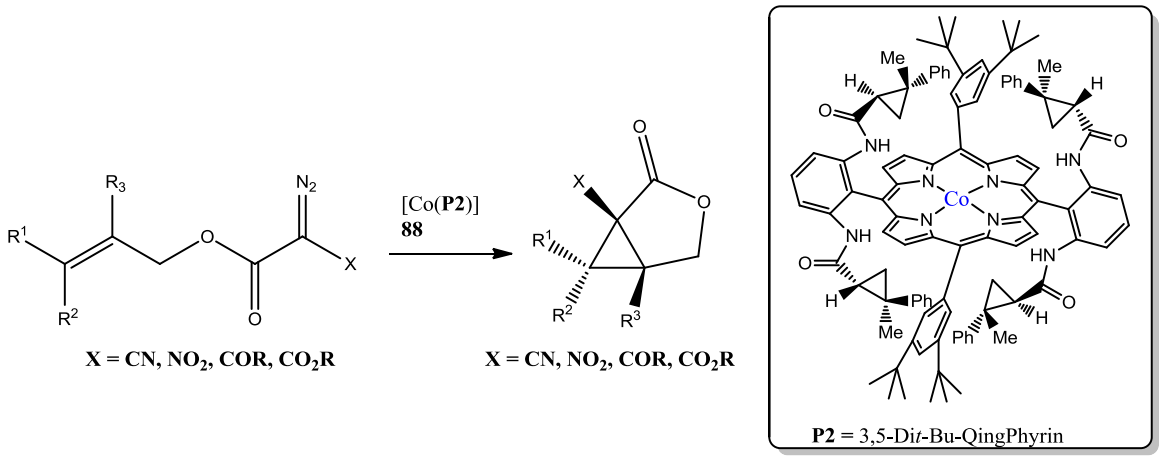


Scheme 3.17

Table 3.7

Entry	R	Catalyst	Yield (%)	ee (%)
1	Ph	PyBOX **83**	86	77
2	Ph	BPI **86**	83	93
3	Ph	(Rh^{II}/pheox) **87**	99	97
4	Ph	Co(II)-Schiff base **84**	67	97
5	*p*-ClC_6H_4	BPI **86**	81	93
6	*p*-ClC_6H_4	Co(II)-Schiff base **84**	72	98
7	*p*-$MeOC_6H_4$	BPI **86**	79	93
8	*p*-$MeOC_6H_4$	(Rh^{II}/pheox) **87**	98	83
9	*p*-$MeOC_6H_4$	Co(II)-Schiff base **84**	93	96

Zhang has demonstrated impressive enantiocontrol in the intramolecular cyclopropanation of α-diazoacetates using a Co(II)-based metalloradical catalyst **88** on a diverse range of substrates (**Scheme 3.18**).[90] Allyldiazoacetates, particularly those with α-acceptor substituents, generated the bicyclic lactones in high yields with excellent stereoselectivities (**Table 3.8**). The author applied an iterative approach in the development of the chiral Co(II) metalloradical catalyst [Co(**P2**)] **88**. Heterocycles such as indole and furans have also been used as α-diazoacetate substrates, opening up the spectrum of potential substrates compatible with this methodology.



88

Scheme 3.18

Table 3.8

Entry	R^1	R^2	R^3	X	Yield (%)	ee (%)
1	H	C_6H_5	H	H	95	99
2	H	C_6H_5	H	Me	82	73
3	H	C_6H_5	H	CO_2Et	99	90
4	H	C_6H_5	H	COMe	63	99
5	H	C_6H_5	H	NO_2	95	89
6	H	C_6H_5	H	CN	99	96
7	H	*p*-*t*-BuC_6H_4	H	CN	99	96
8	H	*p*-MeC_6H_4	H	CN	99	98
9	H	*p*-BrC_6H_4	H	CN	99	95
10	H	*p*-$CF_3C_6H_4$	H	CN	99	95
11	H	Furan	H	CN	51	92
12	H	*N*-BocIndole	H	CN	93	91

3.3.2.2. Preparation of allylic α-diazoacetates

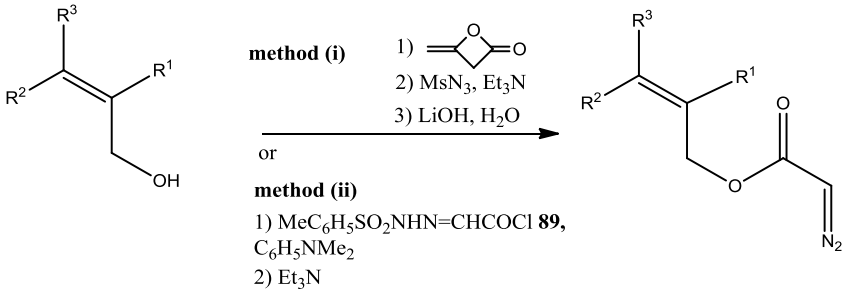
During the course of this research, known allylic α-diazoacetates **97-100** previously reported for intramolecular cyclopropanation were prepared.[81,86] The subsequent transformations were undertaken using mild conditions involving rhodium(II) catalysts in dichloromethane at room

temperature. It was envisaged at the outset that the enantioselectivities of these bicyclic products would be investigated using chiral stationary phase HPLC analysis, allowing comparison to values reported using chiral Doyle's rhodium(II) carboxamidate catalysts[81] and Katsuki's cobalt(II)-Schiff base catalyst (**Section 3.3.2.1**).[86]

Preparation of α-diazoacetates from alcohol precursors has been described using two methods (**Scheme 3.19**):

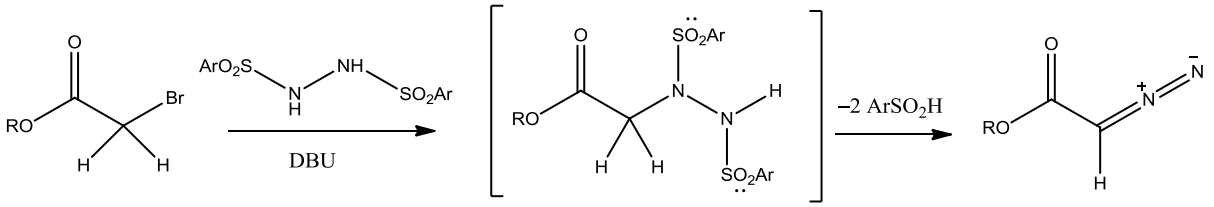
(i) Alkylation using diketene, followed by diazo transfer and subsequent deacylation,[91] or

(ii) Use of the House-Blankley reagent **89** (**Section 1.2.1.7**)[92] with *N,N′*-dimethylaniline and triethylamine (Corey and Myers' modification).[93]



Scheme 3.19

In 2007, Fukuyama published work on the formation of α-diazoacetates from their corresponding α-bromoacetates using *N,N′*-ditosylhydrazine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide the products in high yield; a wide scope was observed (**Figure 3.17**).[94] The bromoacetates were obtained by initial treatment of the appropriate alcohol with bromoacetyl bromide. The main advantage to this method is the ease of handling of the stable crystalline *N,N′*-ditosylhydrazine and the range of α-bromoacetates which can be prepared from the alcohol precursors. A point of note on the mechanism (**Scheme 3.20**) of the one-pot synthesis is that it involves a double-elimination, with loss of two molecules of sulfinic acid from the intermediate to afford the desired α-diazocaetates in high yield under mild conditions.



Scheme 3.20: Mechanism of double-elimination of intermediate to form α-diazoacetate

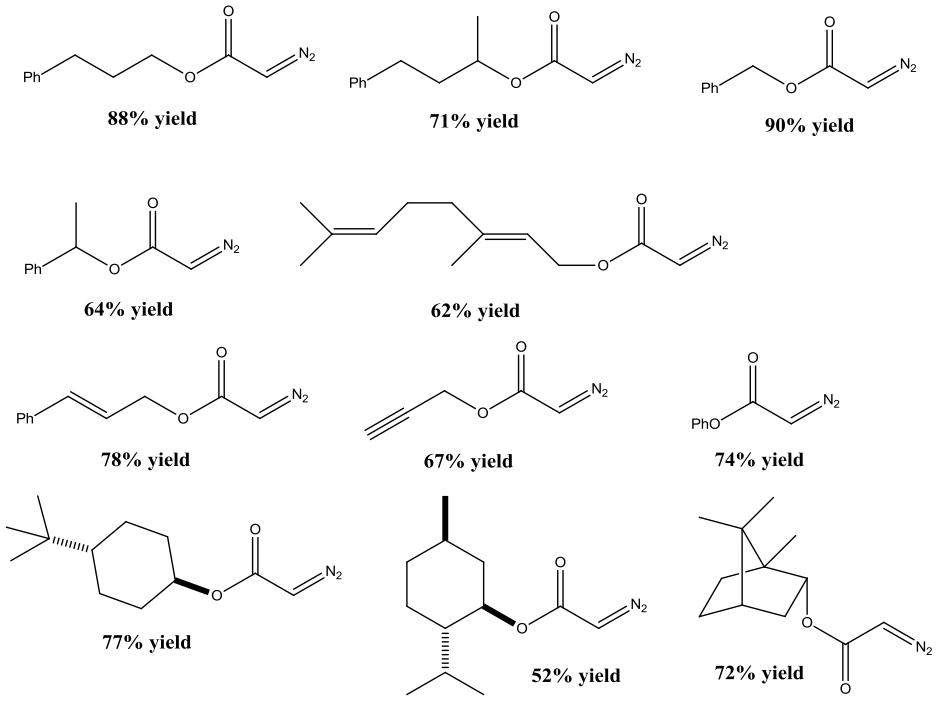
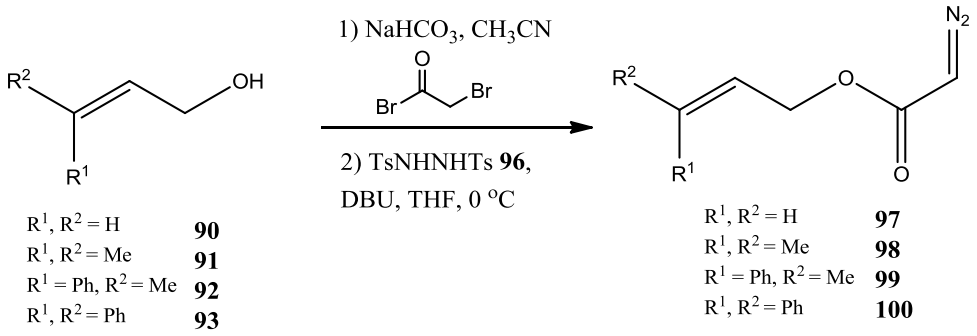


Figure 3.17: Range of α-diazoacetates prepared by Fukuyama method[94]

The Fukuyama method was the chosen route to synthesise α-diazoacetates **97–100** in this project and while the α-diazoacetates were not novel, it was the first time these substrates were prepared using this methodology (**Scheme 3.21**).



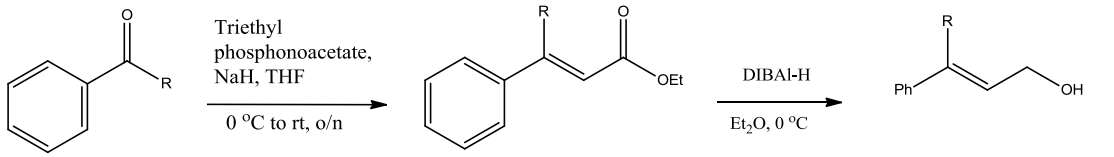
Scheme 3.21

In order to generate the target α-diazoacetates **97–100**, firstly, the alcohol precursors **90-93** had to be prepared. In this work, two of the alcohols **90** and **91** were commercially available whereas the other substrates **92** and **93** had to be prepared. This method involved formation of the α,β-unsaturated esters followed by reduction of the esters to generate the alcohols (**Scheme 3.22**).

The first step in this synthesis involved formation of α,β-unsaturated esters using Horner-Wadsworth-Emmons reaction of acetophenone and benzophenone. A procedure used by Maleczka and co-workers for the synthesis of **92** and **93** was employed here using triethyl

phosphonoacetate, sodium hydride and tetrahydrofuran.[95] The previously reported α,β-unsaturated esters **94** and **95** were isolated after column chromatography in moderate to good yields. Comparison of ^{1}H NMR spectral data from this work and the literature showed that the major isomer of **94** was the *E*-isomer (δ_H ~6.13 ppm, C<u>H</u>CO_2Et), with a trace amount of the *Z*-isomer (δ_H ~5.89 ppm, C<u>H</u>CO_2Et) present in the ^{1}H NMR spectrum of the purified product.[95] ^{1}H NMR spectroscopy of **95** indicated the presence of ~50 mol% benzophenone starting material, identified from higher than expected integration of the aromatic signals. Analysis by infrared spectroscopy provided additional evidence for the presence of unreacted benzophenone with a characteristic stretch identified at ν_{max} 1660 cm^{-1}.

In further work by the same group,[95] reduction of esters **94** and **95** to the corresponding allylic alcohols **92** and **93** was carried out using diisobutylaluminium hydride (DIBAl-H) in ether at 0 °C (**Scheme 3.22**). Following application of that protocol in this work, both the alcohols **92** and **93** were successfully isolated after column chromatography. Formation of the alcohols was confirmed by ^{1}H NMR and infrared spectroscopy, with the loss of the ester functional group and the emergence of the O–H signal in the ^{1}H NMR spectrum (δ_H 1.40 ppm **93**). Allylic alcohol **92** was assigned as the *E*-isomer (δ_H ~5.97 ppm, C<u>H</u>CH_2OH) by comparison to ^{1}H NMR spectral data described by Maleczka[95] and Arai,[96] with a trace amount of *Z*-isomer (δ_H ~5.72 ppm, C<u>H</u>CH_2OH)[97] also present in the ^{1}H NMR spectrum of the purified product. The stretching frequency ascribed to the O–H bond was identified in the infrared spectrum of **92** and **93** (ν_{max} 3327 cm^{-1} **92** and 3358 cm^{-1} **93**).



R = Me, Ph

R = Me, 59% yield **94**

R = Ph, 86% yield **95** (contaminated product contains ~50 mol% benzophenone

R = Me, 97% yield **92**

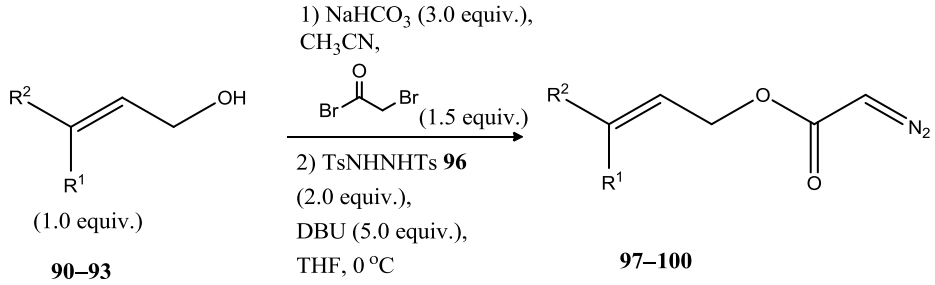
R = Ph, 54% yield **93**

Scheme 3.22

The allylic alcohols **90-93** were then utilised as substrates for Fukuyama's procedure involving preliminary formation of α-bromoacetates prior to the synthesis of the α-diazoacetates.

The α-bromoacetate precursors were constructed by reaction of the alcohol (1.0 equiv.) with bromoacetyl bromide using sodium bicarbonate and freshly distilled acetonitrile as solvent. The reaction was carried out at 0 °C and was complete after 10 min, with the bromoacetate isolated after an acidic workup. The α-bromoacetate intermediates were brought forward without further purification and the next step involved addition of a THF solution of *N*,*N*′-ditosylhydrazine **96** slowly over 15 min to a stirred solution of the α-bromoacetate and DBU (5.0 equiv.) at 0 °C (**Scheme 3.23**). Purification of the crude material was carried out using

silica gel column chromatography, whereas Fukuyama and co-workers used neutral silica gel in their purification of the α-diazoacetates.[94] Spectral characteristics for α-diazoacetates **97-100** were consistent with the literature,[80,86] with a characteristic diazo stretch at ν_{max} ~2112 cm^{-1} observed in the infrared spectrum and a broad singlet corresponding to the proximal hydrogen (C<u>H</u>N_2) identified at δ_H ~4.76 ppm in the ^{1}H NMR spectrum. The α-diazoacetates synthesised **97-100**, as well as the respective yields are summarised below (**Table 3.9**).



Scheme 3.23

Table 3.9

Entry	R^1	R^2	Alcohol	α-diazoacetate	Yield (%)[a]
1	H	H	**90**	**97**[81]	30
2	Me	Me	**91**	**98**[81]	47
3	Ph	Me	**92**	**99**[86]	42
4	Ph	Me	**92**	**99**[86]	22[b]
5	Ph	Ph	**93**	**100**[86]	32

[a] Isolated yield after column chromatography.
[b] Reaction conditions involved 1.2 equiv. DBU and CH_3CN as solvent

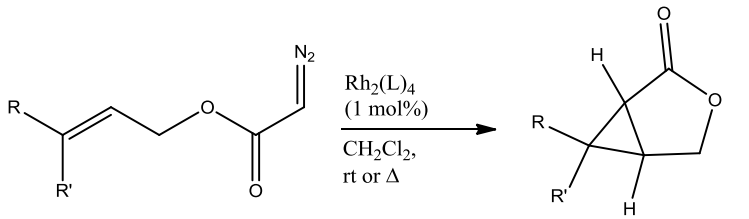
The α-diazoacetates **97-100** were synthesised following Fukuyma's standard conditions (**Table 3.9**, entries 1,2,3 and 5), however, on one occasion (**Table 3.9**, entry 4), slightly modified conditions were explored employing CH_3CN in place of THF and only a slight excess of DBU (1.2 equiv. *cf.* 5.0 equiv.) resulting in decreased yield relative to the standard conditions. While the purified α-diazoacetates were prepared in lower yields (**Table 3.9**) than reported in previous syntheses by Doyle[80,81] and Katsuki (**Scheme 3.18**, method 1),[86] this is the first synthesis of α-diazoacetates **97-100** using Fukuyama's two-step protocol.[94]

3.3.2.3 Formation of 3-oxabicyclo[3.1.0]hexan-2-ones

Although synthesis of the α-diazoacetates **97-100** proved straightforward, intramolecular cyclopropanation presented significant issues which is possibly indicated by lack of precedent regarding use of α-diazoacetates with rhodium(II) carboxylate catalysts. At the outset of this portion of the project, it was decided to use known substrates applicable for intramolecular cyclopropanation and for which chiral HPLC conditions have previously been established for

the corresponding cyclopropyl lactones.[80,81,86] Doyle and co-workers have previously carried out successful intramolecular cyclopropanation of **97** and **98**,[81] while Katsuki has amply demonstrated cyclopropanation of substrates **99** and **100** (**Scheme 3.24**).[86]

Much of the work on the α-diazoacetates **99** and **100** by Katsuki has involved Cobalt(II) and (ON^+/Ru(II)(salen) complexes,[86] while rhodium(II) carboxamidates were applied to homoallylic α-diazoacetates **97** and **98** investigated by Doyle.[81] Prior to this work, there were no reports of use of rhodium(II) carboxylates for intramolecular cyclopropanation with any of the substrates **97-100** to generate cyclopropanes **101-104**.



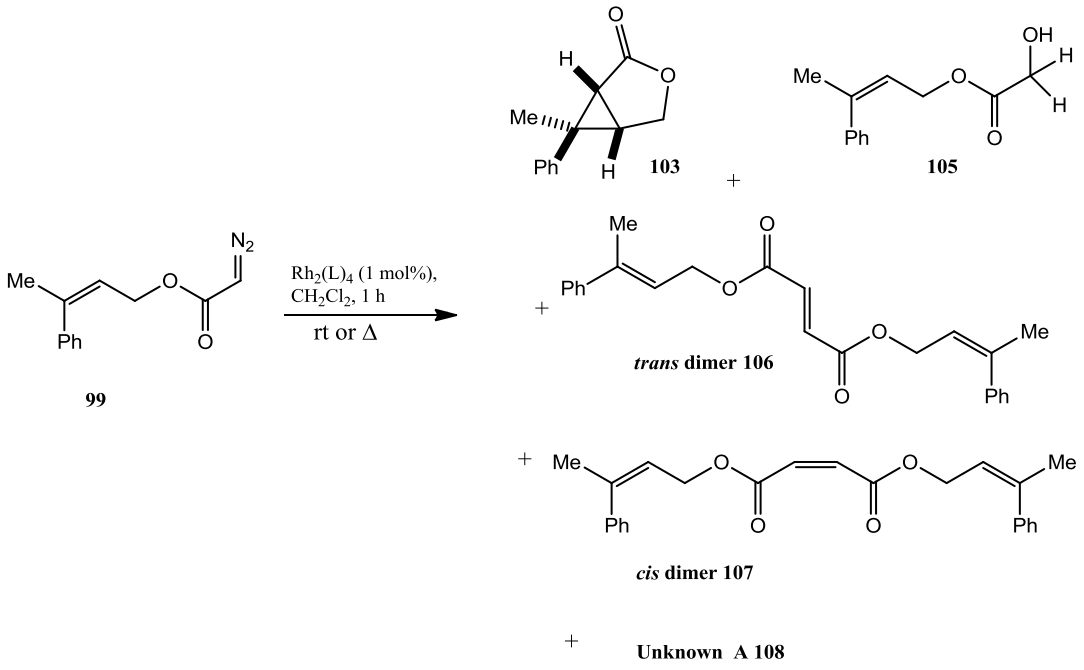
R = H, R' = H **97**
R = Me, R' = Me **98**
R = Me, R' = Ph **99**
R = Ph, R' = Ph **100**

R = H, R' = H **101**
R = Me, R' = Me **102**
R = Me, R' = Ph **103**
R = Ph, R' = Ph **104**

Scheme 3.24

In this study, the two main substrates initially investigated were **98** and **99** since relevant HPLC data and purification procedures were described for the bicyclic lactones **102** and **103** obtained *via* intramolecular cyclopropanation. Preliminary work involved attempting the cyclopropanation of substrate **99** in the presence of $Rh_2(OAc)_4$ **1**, $Rh_2(oct)_4$ **4** or the enantiopure Rh_2(*S*-PTTL)$_4$ **13** catalyst. The reactions were carried out at room temperature or heated under reflux (**Scheme 3.25**). This was undertaken with the objective of successfully carrying out these transformations using rhodium(II) carboxylates to effect cyclopropanation, with structural confirmation by comparison with literature data,[81,86] prior to employment of Ford's novel chiral rhodium(II) carboxylates. Addition of the α-diazoacetate was carried out over 30 min and consumption of the α-diazoacetate starting material was confirmed after 1 h, as determined by infrared spectroscopy and TLC analysis. However, while cyclopropane **103** was seen at low levels in some of the crude product mixtures, the isolation of a pure sample of cyclopropane **103** proved challenging.

Purification by flash chromatography resulted in the isolation of multiple products from the cyclisations and the range of products obtained from this transformation are summarised below (**Scheme 3.25**).



Scheme 3.25

The crude product ratios and isolated yields, where feasible using $Rh_2(OAc)_4$ **1**, $Rh_2(oct)_4$ **4** and Rh_2(*S*-PTTL)$_4$ **13** catalysts are summarised below (**Table 3.10**).

Table 3.10 *Rhodium(II)-catalysed intramolecular cyclopropanations of* **99**[a]

Entry	Catalyst	Temp.	Yield (%)[b]	Crude ratio 103 : 105 : 106 : 107 : 108	Purified ratio 103 : 105
1	Rh_2(*S*-PTTL)$_4$ **13**	rt	42	n/a[c] : n/a[c] : – : – : –	1.0[d] : 0.89[d]
2	$Rh_2(OAc)_4$ **1**	rt	63	– : 19.0[e] : 1.0[e,f] : 1.22[e,f] : –	– : –
3	$Rh_2(oct)_4$ **4**	rt	54	Trace[e] : 14.1[e] : 1.0[e,f] : 1.17[e,f] : 3.21[e]	– : –
4	Rh_2(*S*-PTTL)$_4$ **13**	reflux	52	n/a[c] : n/a[c] : – : – : –	1.0[d] : 2.19[d]

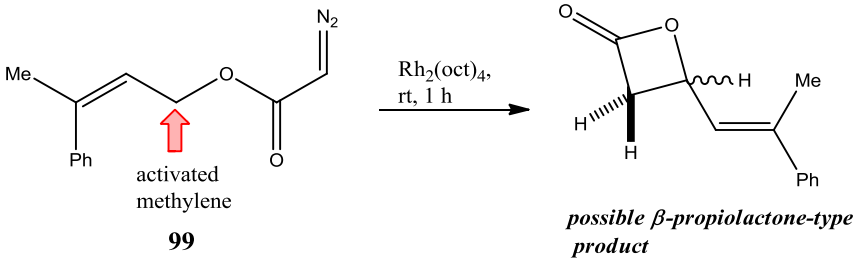
[a] Reaction conducted using the general procedure for rhodium(II)-catalysed intramolecular cyclopropanation reactions.
[b] Combined yield of all isolated products from the reaction mixture.
[c] In this reaction, n/a refers that the crude ratios were not determined.
[d] Cyclopropane **103** not isolated cleanly and co-eluted with O–H insertion product **105**. The ratio is assigned from integration of the purified mixture and not from ^{1}H NMR of the crude material.
[e] Ratio assigned by integration of the crude reaction mixture.
[f] Signals at δ_H 6.91 ppm and δ_H 6.30 ppm in the crude mixture were assigned as (*E*) and (*Z*) dimers **106** and **107** on the basis of comparison with literature data for diethyl fumarate and diethyl maleate [(*E*) δ_H 6.85 ppm and (*Z*) δ_H 6.24 ppm].[98]

The bicyclic lactone **103** was observed to co-elute with the water insertion product (α-hydroxyketone) **105** using Rh_2(*S*-PTTL)$_4$ **13** as catalyst (**Table 3.10**, entries 1 and 4). A distinctive broad singlet, corresponding to the water insertion product was observed at δ_H ~2.50 ppm for the cyclisation using $Rh_2(oct)_4$ **4** at room temperature (**Table 3.10**, entry 3). Curiously, the signal ascribed to COC$\underline{H}_2$OH for entries 3 and 4 was identified at δ_H ~4.20 ppm *cf.* δ_H ~4.28 ppm observed for entries 1 and 2. The presence of residual ethyl acetate may be responsible for the disparity of the chemical shifts for the methylene group. While the

reactions were conducted under nitrogen, Schlenk conditions were not employed (**Table 3.10**, entries 1, 3 and 4), which may have resulted in the presence of adventitious water, which can react with the metallocarbenoid to generate the α-hydroxyketone **105**. This is a known side pathway in α-diazoketone cyclisations, especially at ambient temperature and similar products were previously reported by Buckley in investigations of the intramolecular Buchner reaction.[99] Mass spectrometry also confirmed formation of the α-hydroxyketone **105**, with detection of the molecular ion in the nominal mass spectrum, m/z (ES+) $[M+H]^+$ 207.5 and further confirmation in the high resolution analysis, $[M+H]^+$ 207.1228.

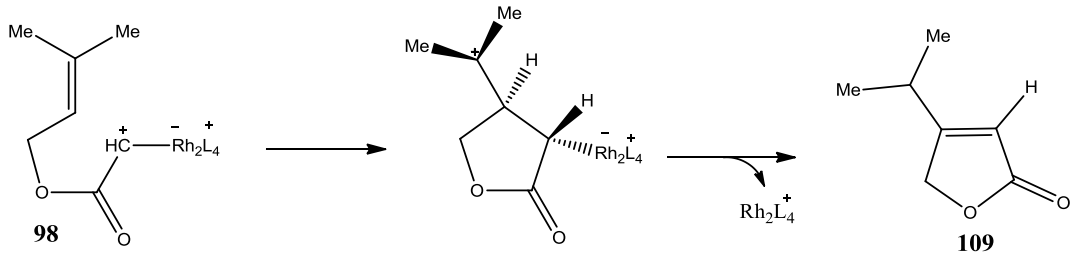
Schlenk conditions were used in one case in the presence of $Rh_2(OAc)_4$ (**Table 3.10**, entry 2), which still resulted in formation of α-hydroxyketone **105** as the major product in the crude ^1H NMR spectrum, as well as identification of both *trans* **106** and *cis* **107** dimers. The *trans* dimer **106** was isolated following flash chromatography in 5% yield. Assignment of the *trans* and *cis* dimers in the crude reaction mixture was by comparison with signals for diethyl fumarate and diethyl maleate in the literature (δ_H 6.85 *vs.* 6.24 ppm for *trans* and *cis* respectively).[98]

For reaction in the presence of $Rh_2(oct)_4$ **4** (**Table 3.10**, entry 3), a previously unseen product was isolated by flash chromatography and this very polar product gave a complex splitting pattern in the ^1H NMR spectrum due to enhanced multiplicity of the signals. It could be speculated that unknown A **108** might resemble a β-propiolactone-type compound, which can be envisioned to arise *via* C–H insertion to the methylene group, due to the directing effect of the α-substituted oxygen (**Scheme 3.26**). Although carbenoid-mediated C–H insertion into activated methylene groups, generating 4-membered lactones is precedented,[100,101] integration of the signals in the ^1H NMR spectrum did not conclusively indicate that this is the case and further analysis of this compound will need to be undertaken to definitively assign it. Additionally, the presence of common signals to the dimer **106** and α-hydroxyketone **107** suggests the atom connectivity of the chain is maintained in the unknown product **108**.



Scheme 3.26

A side product noted by Doyle and co-workers in their rhodium(II)-catalysed transformations of the dimethyl substituted α-diazoketone **98** was the butenolide **109**, which is generated from 1,2-hydride shift from an originally formed tertiary carbocation intermediate (**Scheme 3.27**).[32] While this pathway was observed in Doyle's studies, this does not appear to resemble Unknown A **108** in this work.



Scheme 3.27: Butenolide side product from work by Doyle[32]

^{1}H NMR spectra for the isolated *trans* dimer **106**, isolated water insertion product **105**, mixture of cyclopropane **103**/water insertion product **105** and isolated Unknown A **108** are shown below (**Figure 3.18**).

In the figure below (**Figure 3.18**), the characteristic signals for each compound are highlighted; peaks for the *trans* dimer **106** are identified by the red region, peaks for the α-hydroxyketone **105** by the blue region, signals for the cyclopropane **103** by the green region and signals for Unknown A **108** by the purple region.

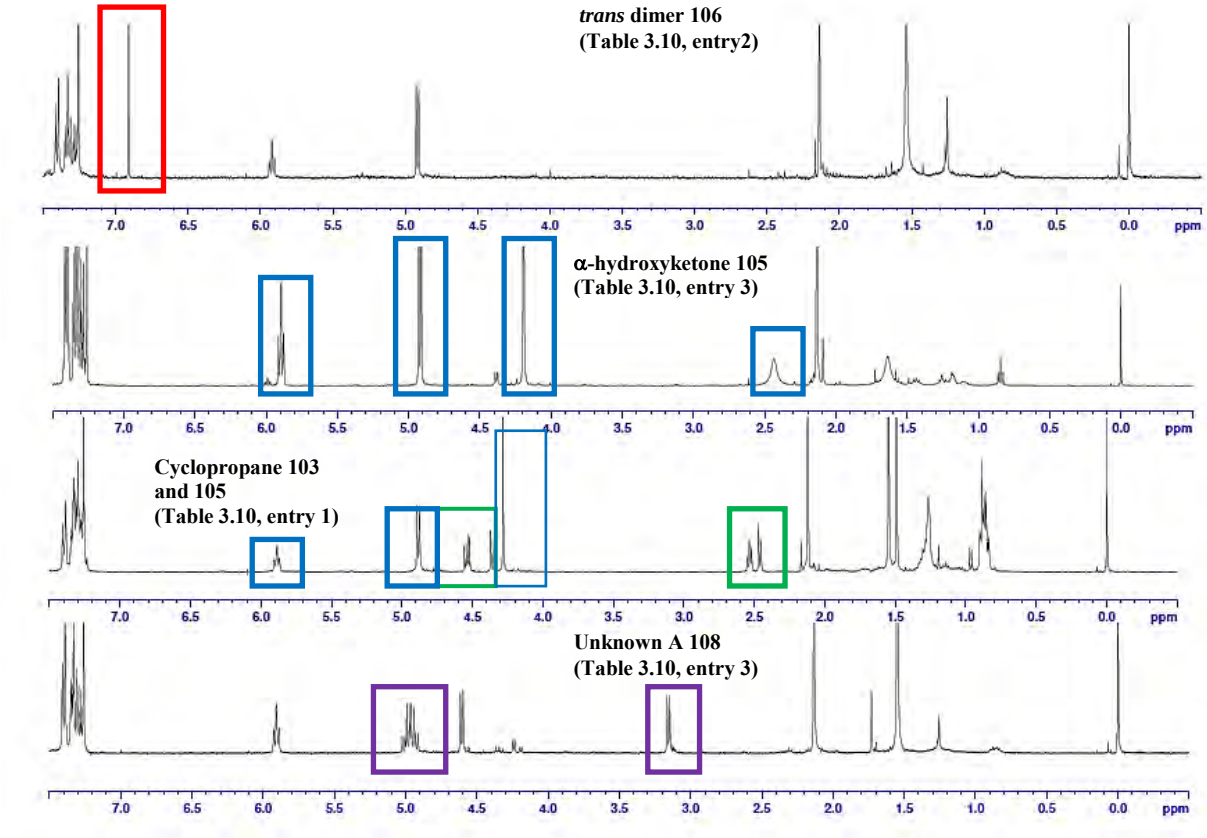
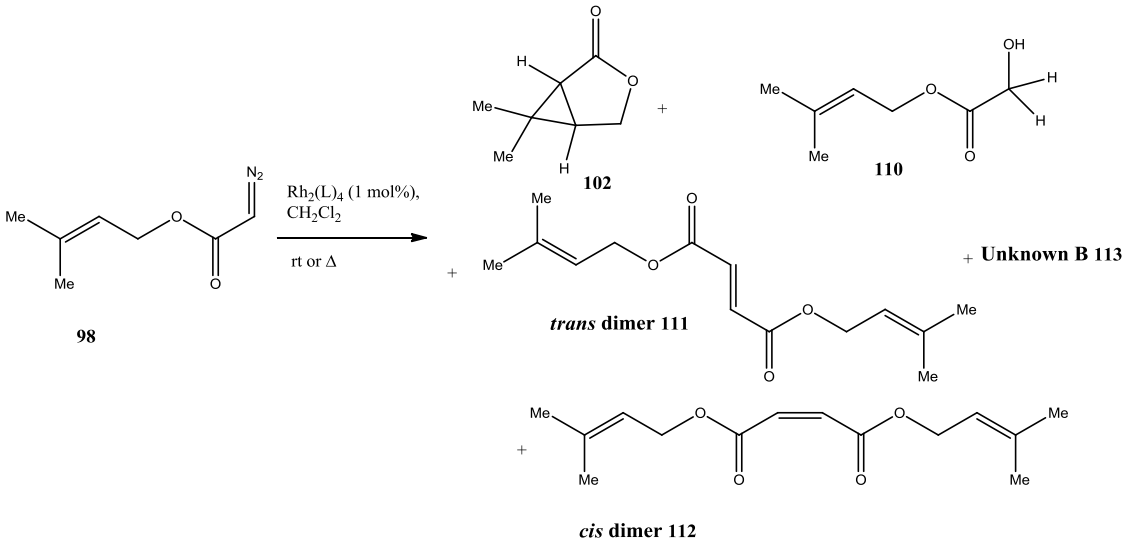


Figure 3.18 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of isolated sample of 106, isolated sample of 105, co-eluting mixture of 103/105 and isolated sample of 108

The next substrate examined was 3-methylbut-2-en-1-yl 2-diazoacetate **98** (**Scheme 3.28**) and in a similar manner to **99**, initial reactions (entries 1 and 2) conducted at room temperature displayed no obvious indication of formation of the desired bicyclic lactone **102**, instead resulting in the formation of the α-hydroxyketone **110** and minor amounts of both *trans* **111** and *cis* **112** dimers (**Table 3.10**, entries 1 and 2). It is worth noting that the signal ascribed to the methylene group adjacent to the hydroxyl moiety, C$\underline{H_2}$OH, gave a lower integration than expected in the crude ^{1}H NMR spectrum (**Table 3.10**, entry 2). For entries 1 and 2, all attempts to generate the cyclopropanes involved conducting the reaction at room temperature and carrying out addition of the α-diazoacetate over ~1 h. In this work, purification involved flash chromatography, which in retrospect may not be ideal conditions to isolate the volatile fused cyclopropyl lactones.



Scheme 3.28

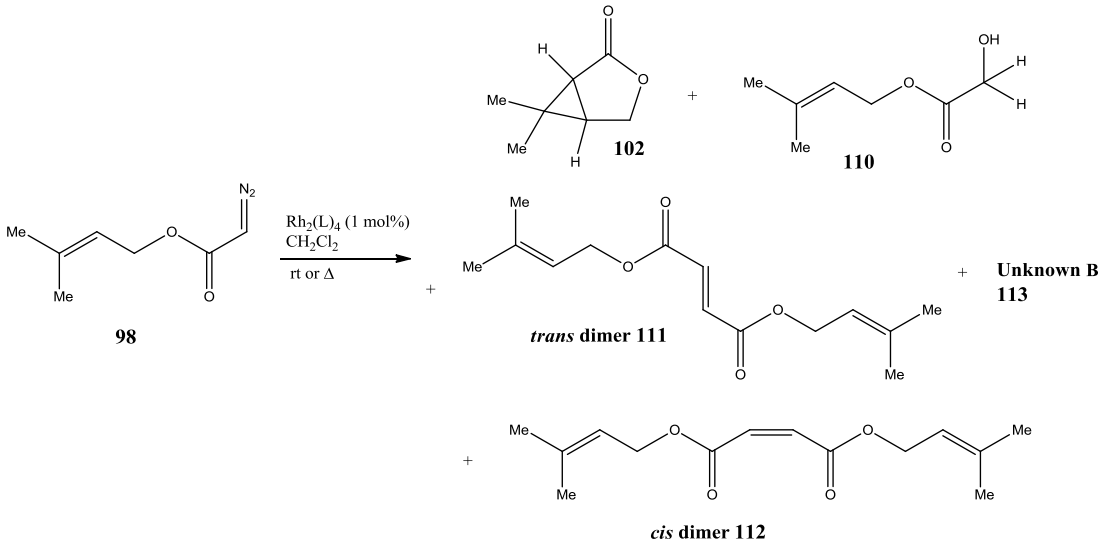
In contrast, Doyle's work with compound **98** involved conducting the reaction under reflux conditions and a slow addition of the α-diazocarbonyl compound over 6–12 h. The purification in Doyle's work was different from efforts in this work as Doyle and co-workers used Kugelrohr distillation to purify the bicyclic lactones. With this in mind, intramolecular cyclopropanation of **98** using the same conditions as Doyle previously employed using different rhodium(II) catalysts was subsequently investigated (entries 3 and 4).[81]

Utilising a longer period for addition of the α-diazoacetate and heating the reaction mixture under reflux conditions, the cyclopropane **102** could be identified from the crude ^{1}H NMR spectroscopy, as well as the formation of the *trans* dimer **111** and the *cis* dimer **112** (**Table 3.10,** entry 3). The presence of the *trans* dimer **111** was confirmed by nominal mass spectrometry on a sample isolated after column chromatography, with identification of the molecular ion, m/z (ES+) 253.4. For these reactions, there was a noticeable absence of any water insertion product **110**. Unfortunately, a clean sample of the cyclopropane was not

successfully isolated, though clean samples of both the *trans* and *cis* dimers **111** and **112** were recovered after chromatography in 11% and 6% isolated yield respectively.

Since efforts involving flash chromatography failed to successfully purify and isolate the cyclopropane **102**, the next approach involved Kugelrohr distillation to isolate the intramolecular cyclopropanation product (**Table 3.11**, entry 4). Encouragingly, the purified product was isolated as a colourless oil and contained signals corresponding to the cyclopropane **102**. The characteristic signals in the ^{1}H NMR spectrum were observed at δ_H 1.95 (dd, *J* 6.0, 0.8 Hz) and 2.05 (t, *J* 6.4 Hz) ppm for the cyclopropane ring while the signals ascribed to the lactone moiety were seen at δ_H 4.15 (d, *J* 9.6 Hz) and 4.37 ppm (dd, *J* 10.0, 5.6 Hz). While these values were in excellent agreement with the literature and prove the formation of the cyclopropane **102**,[81] there was a significant amount of an Unknown B **113** observed in 1.0 : 1.03 ratio of **113** : **102** (**Table 3.11**, entry 4). Further evidence for successful formation of the cyclopropane **102** was achieved by nominal mass spectrometry with the molecular ion detected at m/z (ES+) $[M+H]^+$ 127.3. It was thought that the impurity Unknown B **113** would impact on chiral HPLC analysis attempted for the bicyclic lactone **103** and consequently no further work was carried out on this compound.

Table 3.11 *Rhodium(II)-catalysed intramolecular cyclopropanation of* **98**[a]



Entry	Catalyst	Temp.	Yield (%)[b]	Crude ratio 102 : 110 : 111 : 112 : 113	Purified ratio 102 : 111 : 112 :113
1	Rh_2(*S*-DOSP)$_4$ **9**	rt	29	n/a[c] : n/a[c] : n/a[c] : – : –	3.46[d] : 1.0[d] : 1.61[d] : –
2	Rh_2(oct)$_4$ **4**	rt	34	– : 29.8[e] : 1.0[e,f] : 1.0[e,f] : –	– : – : – : –
3	Rh_2(oct)$_4$ **4**	reflux	53	1.0[e] : – : 1.01[e,f] : 1.05[e,f] : –	– : – : – : –
4	Rh_2(*S*-PTTL)$_4$ **13**	reflux	73	1.0[e] : – : 0.06[e,f] : 0.18[e,f] :1.51[e]	1.03[d] : – : – : 1.0[d]

[a] Reactions conducted using the general procedure for rhodium(II)-catalysed intramolecular cyclopropanation.
[b] Combined yield of all isolated products from the reaction mixture.
[c] In this reaction, n/a refers that the crude ratios were not determined.
[d] Ratio is assigned from ^{1}H NMR integration of the purified product and not from integration of the crude material. Signal for C$\underline{H_2}$OH appears to be present at δ_H 4.23 ppm.
[e] Ratio is based on ^{1}H NMR integration of the crude reaction mixture.

[f] Signals at δ_H 6.85 ppm and δ_H 6.22 ppm in the crude mixture were assigned as *trans* and *cis* dimers **111** and **112** on the basis of comparison with literature data for diethyl fumarate and diethyl maleate (*trans* δ_H 6.85 ppm and *cis* δ_H 6.24 ppm).[98]

The ^{1}H NMR spectra for the isolated *trans* dimer **111**, mixture of water insertion product **110**/*trans* dimer **111**/*cis* dimer **112** and mixture of cyclopropane **102**/Unknown B **113**, *trans* dimer **111**/*cis* dimer **112** are shown below (**Figure 3.19**).

In the figure below (**Figure 3.19**), the characteristic signals for each compound are highlighted; peak for the *trans* dimer **111** is identified by the red region, peaks for the α-hydroxyketone **110** by the blue region, signals for the *cis* dimer **112** by the yellow region, signals for the cyclopropane **102** by the green region and peaks corresponding to the Unknown B **113** by the purple region.

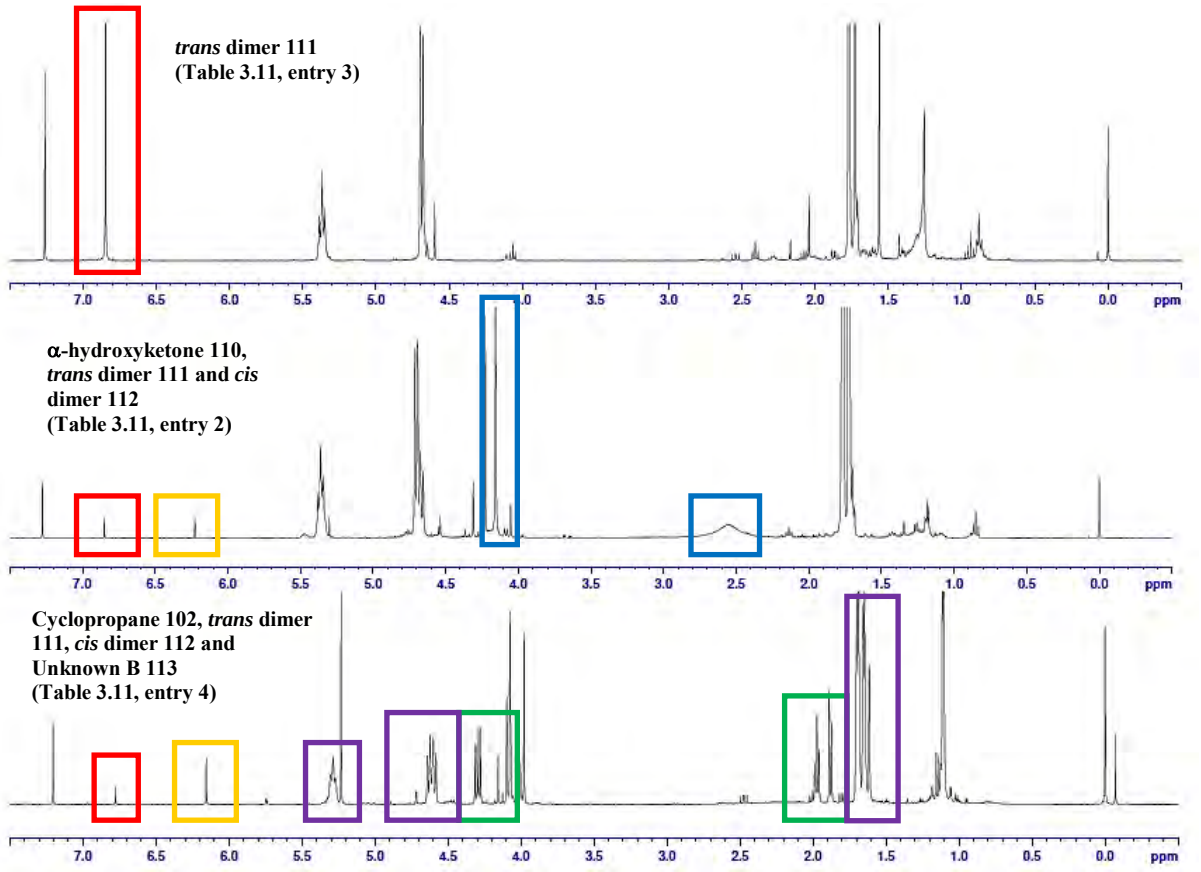


Figure 3.19 ^{1}H NMR spectra (400 MHz, $CDCl_3$) of isolated sample of 110, mixture of 110/111/112 and complex mixture of 102/111/112/113

At this juncture, it is possible that the difficulty in preparing a clean sample of the bicyclic lactones **102** and **103** was due to use of rhodium(II) carboxylates, which may be supported by a lack of literature precedent. Previous reports by Doyle applied chiral rhodium(II) carboxamidates as catalysts for intramolecular cyclopropanations of **97** and **98**,[81] which were particularly effective catalysts for these substrates. With respect to intramolecular

cyclopropanations of **99** and **100**, Katsuki previously employed Co(II)(salen) complexes,[86] with no rhodium(II) catalysis described for these substrates.

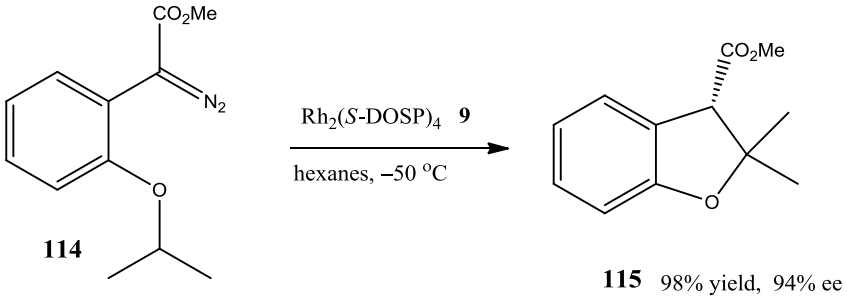
Intramolecular cyclopropanations using Ford's novel chiral rhodium(II) carboxylates were not attempted on α-diazoacetates **97-100** in this work due to the challenges in cleanly isolating cyclopropyl lactones from reactions in the presence of $Rh_2(OAc)_4$ **1**, $Rh_2(oct)_4$ **4** and enantiopure Rh_2(*S*-PTTL)$_4$ **13** catalysts.

3.3.3 Intramolecular Carbon–Hydrogen Insertion (C–H insertion)

3.3.3.1 Background

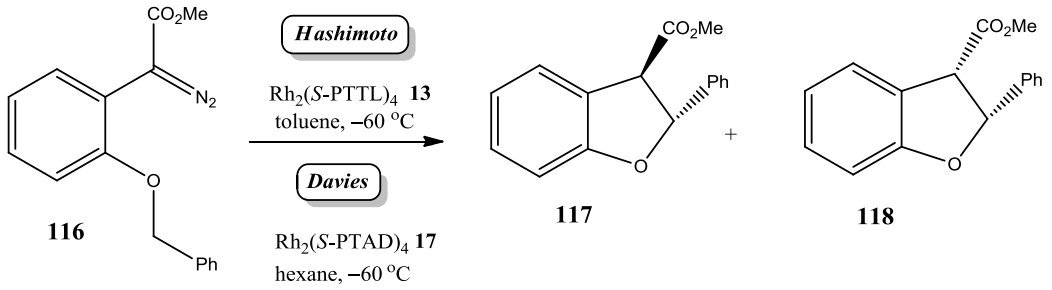
As discussed previously (**Section 1.5.2.1**), intramolecular C–H insertion reactions can be both highly regio- and diastereoselective in the formation of various carbocyclic and heterocyclic ring systems through the use of rhodium(II) carboxylates as catalysts.[102-109] This scope has been broadened through the advent of various asymmetric rhodium(II) catalysts developed by Doyle,[12] McKervey,[14] Hashimoto[15] and Davies.[17]

The groups of Davies in 2001[76] and Hashimoto in 2002[110] have carried out synthesis of dihydrobenzofurans applying C–H insertion as the pivotal step in the process (**Scheme 3.28** and **Scheme 3.29**). From initial screening conditions, it was observed that both the temperature control and solvent choice are important factors; with optimal results obtained at low temperatures (–60 °C) and carrying out the reaction in solvents such as hexanes and toluene. Deviation from the optimised conditions resulted in a markedly reduced product yield as formation of an azine side product increases and this side product can co-elute with the *cis* dihydrobenzofuran.[110] Employing their established Rh_2(*S*-DOSP)$_4$ **9** catalyst in the intramolecular C–H insertion of **114**, Davies *et al.* prepared the dihydrobenzofuran **115** in both excellent yield and enantioselectivity (94% ee) (**Scheme 3.29**).[76]



Scheme 3.29

Hashimoto and co-workers subsequently investigated the cyclisation of the benzyl substituted α-diazoacetate **116**, utilising their Rh_2(*S*-PTTL)$_4$ **13** catalyst, as well as a polymer-supported version of the same catalyst,[111] while Davies' efforts focused on substrate **116** allied with a novel adamantyl catalyst Rh_2(*S*-PTAD)$_4$ **17**.[67] Carbenoid-mediated C–H insertion provided dihydrobenzofurans **117** and **118** in high yields (**Scheme 3.30**). Impressively high diastereomeric excess (30–99 : 1) and excellent enantioselectivities (91–95% ee) were achieved in each case (**Table 3.12**, entries 1, 2 and 4). Use of Rh_2(*S*-PTPA)$_4$ **14** catalyst by Hashimoto resulted in an increased amount of *trans* isomer **117**, with a diastereomeric ratio of 30 : 70 of **117** : **118** observed (**Table 3.12**, entry 3).[110] Interestingly, although **117** was generated as the minor diastereomer under these conditions, a higher enantiopurity was obtained for the sample of **117** than for **118** (80% ee *vs.* 70% ee, **Table 3.12**, entry 3).[110]



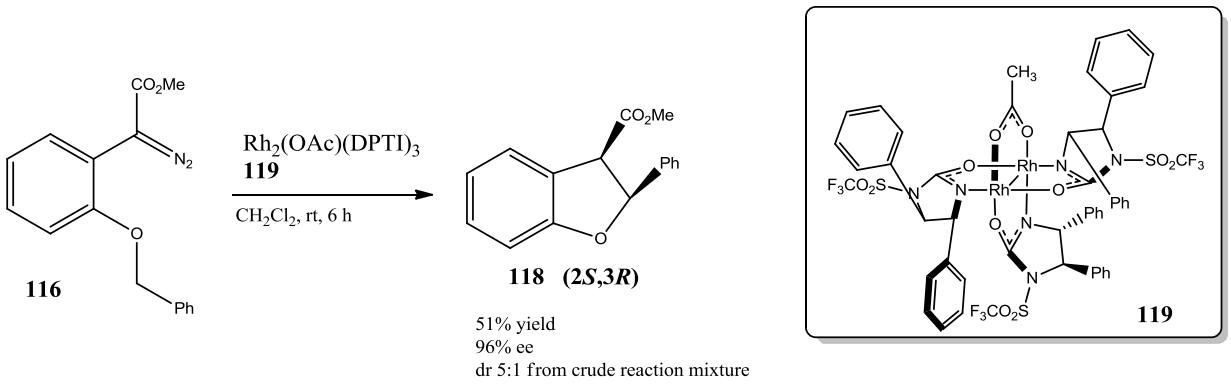
Scheme 3.30

Table 3.12

Entry	Catalyst	Conditions	Yield (%)	*trans/cis*[a] 117 : 118	ee (%) 117	ee (%) 118
1	Rh_2(*S*-PTTL)$_4$ **13**	PhMe, –78 °C	79	1 : >99	–	94[b]
2	Polymer bound **13**	PhMe, –60 °C	85	1 : >99	–	91[c]
3	Rh_2(*S*-PTPA)$_4$ **14**	PhMe, –60 °C	84	30 : 70	80[b]	70[b]
4	Rh_2(*S*-PTAD)$_4$ **17**	hexanes, –60 °C	88	1 : >30	–	95[d]

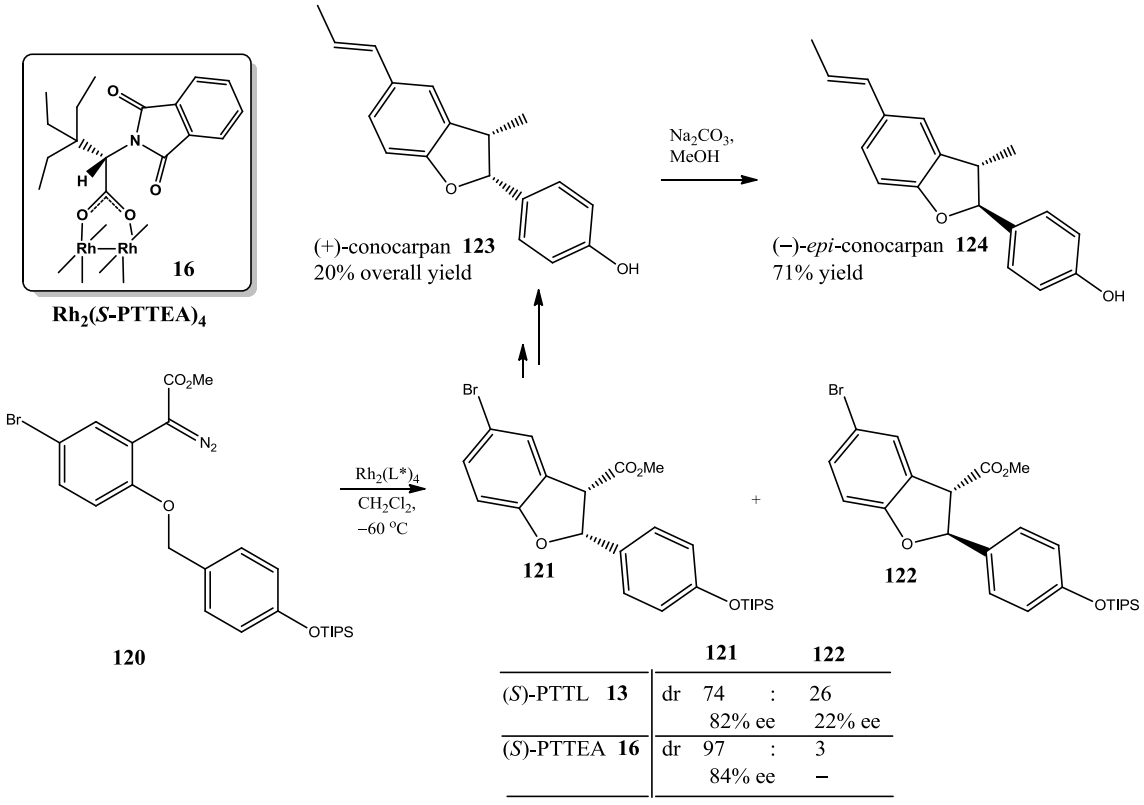
[a] Ratios based on integration of the methoxy ($CO_2C\underline{H}_3$) signals from the ^{1}H NMR spectra of the crude products.
[b] Refers to data from reference [110].
[c] Refers to data from reference [111].
[d] Refers to data from reference [67].

Corey also reported high enantioselectivity for C–H insertions of the same substrate **116** using a novel heteroleptic rhodium(II) catalyst, [(*R*,*R*)-Rh_2(OAc)(DPTI)$_3$] **119** (**Scheme 3.31**),[112] resulting in predominant formation of the *cis* dihydrobenzofuran **118**. The (2*S*,3*R*)-enantiomer was observed as the major enantiomer in Corey's studies, whereas Hashimoto's Rh_2(*S*-PTTL)$_4$ **13** and Davies' Rh_2(*S*-PTAD)$_4$ **17** catalysts provided the (2*R*,3*S*)-enantiomer as the major enantiomer in all cases.[67,110] In Corey's work, the major product was furnished in 51% yield and 96% ee. The minor *trans* isomer **117** was also identified with a *cis*/*trans* ratio of 5 : 1 observed from ^{1}H NMR spectroscopy of the crude product, in contrast to the near exclusive diastereoselectivity achieved in cyclisations involving the Rh_2(*S*-PTTL)$_4$ **13** system.



Scheme 3.31

Stereoselective synthesis of neoliganan natural products using this methodology has been amply demonstrated by Hashimoto and co-workers using Rh_2(*S*-PTTEA)$_4$ **16** catalyst (**Scheme 3.32**).[113] This complex possesses bulky triethylmethyl groups increasing the steric effect of this catalyst with respect to the analogous Rh_2(*S*-PTTL)$_4$ **13**. Treatment of α-diazoacetate **120** in the presence of catalysts **13** and **16** afforded the dihydrobenzofuran products **121** and **122** in high diastereomeric ratio (dr) of 97 : 3 using Rh_2(*S*-PTTEA)$_4$ **16**, while use of Rh_2(*S*-PTTL)$_4$ **13** gave a lower diastereomeric ratio of 74 : 26. The Rh_2(*S*-PTTEA)$_4$ **16** catalyst registered 84% ee for the *cis* isomer **121**, while the related Rh_2(*S*-PTTL)$_4$ **13** system provided enantiopurities of 82% ee for the *cis* isomer **121** and 22% ee for the *trans* isomer **122**. The natural product (+)-conocarpan **123** was successfully prepared in 20% overall yield following a short synthetic sequence from the *cis* dihydrobenzofuran **121**, with the analogous (–)-*epi*-conocarpan **124** generated from epimerisation to the opposite diastereomer.

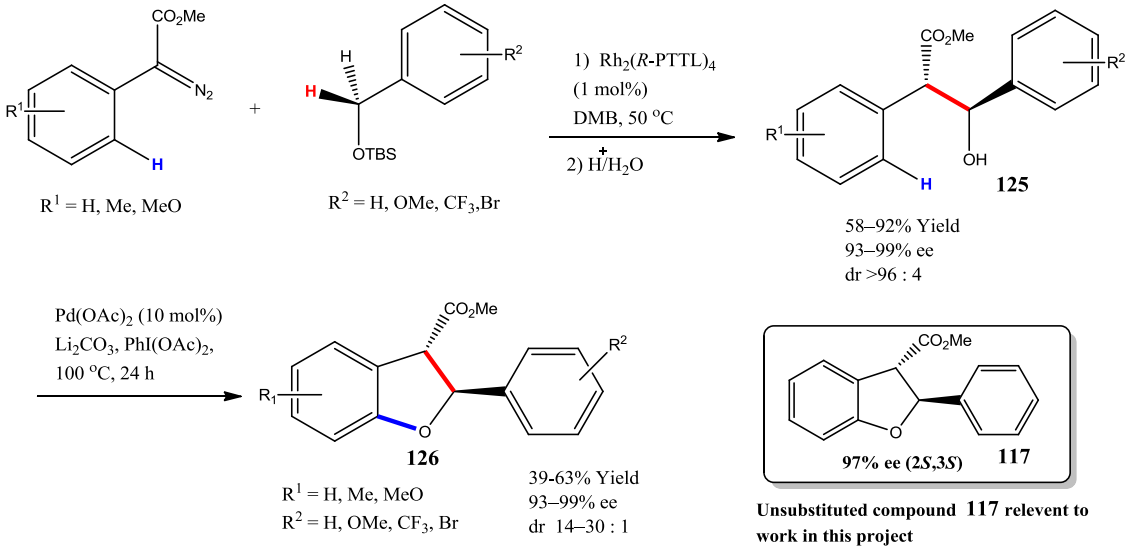


		121		122
(*S*)-PTTL **13**	dr	74	:	26
		82% ee		22% ee
(*S*)-PTTEA **16**	dr	97	:	3
		84% ee		–

Scheme 3.32

Previously, the highest enantiomeric excess for the *trans* isomer **117** was reported by Hashimoto and co-workers at 80% ee using their Rh_2(*S*-PTPA)$_4$ **14** catalyst under optimised conditions. In that work, the (2*R*,3*R*)-enantiomer was observed as the major component.[110] Very recently, collaborative work by Davies and Yu have surpassed this result delivering excellent enantioselectivities of 2,3-dihydrobenzofurans using an alternative approach encompassing sequential C–H functionalisation processes.[114] This strategy combines two distinct C–H functionalisation methods, namely a rhodium(II)-catalysed intermolecular C–H insertion and a palladium(II)-catalysed C–H activation/C–O cyclisation (**Scheme 3.33**). The

intermolecular C–H insertion methodology is a well-established procedure in the Davies group,[115-118] while Yu and co-workers have been exploring the scope and limitations of C–H activation/C–O cyclisation.[119] Upon assembly of the suitable precursor **125** following intermolecular C–H insertion and deprotection to generate an available hydroxyl group, the palladium-catalysed reaction favours the critical ring-closure at the hydrogen in the *ortho* position to the highly functionalised side-chain, as highlighted in blue (**Scheme 3.32**). This streamlined approach allows synthesis of dihydrobenzofurans **126** in high enantiocontrol (93–99% ee). The (2*S*,3*S*)-enantiomer was observed as the predominant enantiomer following chiral HPLC studies undertaken in this work,[114] unlike Hashimoto's studies where the (2*R*,3*R*)-enantiomer was favoured.[110]



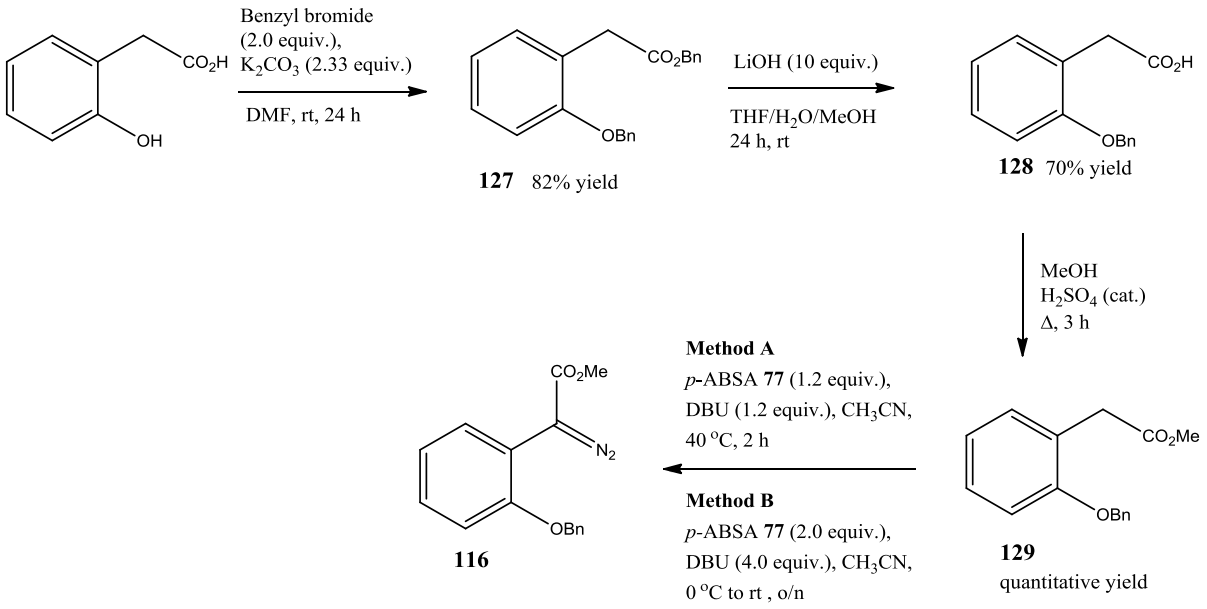
Scheme 3.33

3.3.3.2 Synthesis of methyl 2-[2-(benzyloxy)phenyl]-2-diazoacetate 116

The strategy for formation of α-diazoacetate **116** involved a straightforward four-step synthesis (**Scheme 3.34**). The first step consisted of benzylation of the commercial 2-(2-hydroxyphenyl)acetic acid using benzyl bromide to furnish the dibenzylated ester **127**. Hydrolysis of **127** using lithium hydroxide afforded carboxylic acid **128**, followed by an esterification using methanol and sulfuric acid to generate the appropriate methyl ester **129**. This synthetic route follows that previously carried out by Ford for the preparation of compounds **127-129**,[48] as previous work by Hashimoto,[110] Davies[67] and Corey[112] have not disclosed a synthetic method to prepare methyl ester **129** prior to diazo transfer.

In this work, diazo transfer employed *p*-ABSA **77** as diazo transfer reagent and followed methods outlined by both Ford (Method A)[48] and Hashimoto (Method B).[110] Method B used by Hashimoto is a modification of a procedure originally described by Davies in the synthesis of α-diazoacetate **114**.[76]

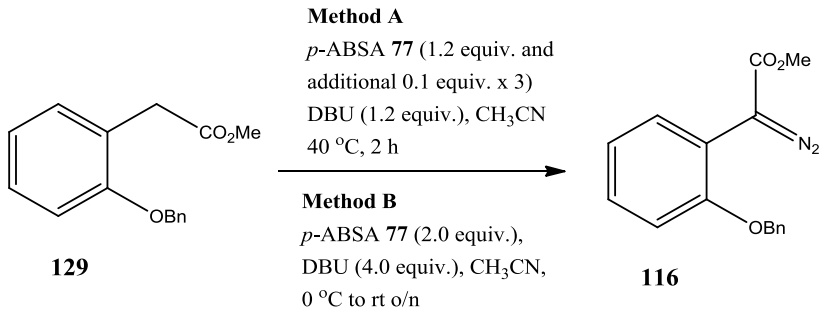
Spectral data for compounds **127-129** was consistent with that described by Ford[48] and previously reported in the literature.[120,121]



Scheme 3.34

The last step was formation of the α-diazoacetate **116** using the diazo transfer method. The particular method employed, as well as the mass recovery and overall yield is summarised below (**Table 3.13**).

Table 3.13



Entry	Procedure	Conditions	Mass Recovery (%)[a,b]	Yield 116 (%)[c]
1	Method A	40 °C, 2h	64 (contains 41 : 59 mixture of **116** and starting material **129**)[a]	–
2	Method B using mixture of **116** and starting material **129** obtained from entry 1	rt, o/n	81 (based on mixture from entry 1)[b]	47 overall yield based on starting material used for entry 1

[a] Mass recovery of crude product

[b] Mass recovery of purified product.

[c] Isolated yield of **116** following Method A and B on the single sample of **129**

In this work, the method employed was the same as previously used for the preparation of methyl phenyldiazoacetate **76**, following conditions outlined by Ford (Method A).[48] The reaction conditions consisted of carrying out the reaction at 40 °C for 2 h and addition of *p*-ABSA **77** (1.2 equiv. and additional 0.1 equiv. × 3), followed by a modified workup to generate the crude α-diazoacetate **116**. In a similar manner to attempted preparation of **76** using Ford's conditions, infrared spectroscopy of the crude product highlighted the presence of starting material **129** with a signal observed at ν_{max} 1736 cm^{-1}, as well as the stretch ascribed to the α-diazoacetate **116** at ν_{max} 1702 cm^{-1}. The crude product was found to contain a mixture of both α-diazoacetate product **116** and unreacted starting material **129** (~41 : 59 of **116** : **129**) in 64% mass recovery (**Table 3.13**, entry 1). Characteristic signals observed in the ^{1}H NMR spectrum, which was run in $CDCl_3$ included three singlets at δ_H 3.64, 3.69 and 5.09 ppm corresponding to **129** by comparison with literature data[121] and two singlets at δ_H 3.82 and 5.11 ppm, which were assigned to the α-diazoacetate **116**.

The crude mixture (~41 : 59 of **116** : **129**) was re-exposed to diazo transfer conditions outlined by Hashimoto (Method B). A slightly modified version of this method was applied in this project using 2.0 equiv. *cf.* 3.0 equiv. *p*-ABSA **77** employed in Hashimoto's work (**Table 3.13**, entry 2).[76] This procedure involved addition of DBU (4.0 equiv.) in acetonitrile to a solution of the crude mixture (~41 : 59 of **116** to **129**) and diazo transfer reagent **77** in acetonitrile at 0 °C, with the reaction mixture warmed to room temperature overnight.

Following analysis by ^{1}H NMR spectroscopy of the crude product, it was ascertained that no starting material was present in the reaction mixture and this was subsequently purified by column chromatography. The pure α-diazoacetate **116** was isolated in 81% mass recovery based on the mixture obtained from Method A and was isolated as a viscous orange oil in 47% overall yield based on the starting material **129** used for Method A (**Table 3.13**, entry 2). Analysis by infrared spectroscopy, as well as ^{1}H NMR and ^{13}C NMR spectroscopy in DMSO-d_6, (previously reported in C_6D_6),[110] were consistent with formation of the desired α-diazoacetate **116** by comparison to reported literature values (**Figure 3.20**).[110] As the purified sample of **116** was found to be sparingly soluble in $CDCl_3$, DMSO-d_6 was used as solvent for ^{1}H and ^{13}C NMR spectroscopic analysis in this work.

Therefore, diazo transfer to generate **116** is best effected as described by Hashimoto, at room temperature overnight and using a higher number of equivalents of both DBU and *p*-ABSA **77**.[110]

Characteristic infrared stretching frequencies were identified for the diazo and ester moieties at ν_{max} 2098 and 1702 cm^{-1} respectively, which were in close agreement with the literature data of ν_{max} 2099 and 1701 cm^{-1}.[110] Comparative ^{1}H and ^{13}C NMR analysis using samples run in both C_6D_6 and DMSO-d_6 showed good general correlation with the exception of the signals for the methyl group, δ_H 3.34 ppm in C_6D_6[110] *cf.* δ_H 3.74 ppm in DMSO-d_6 and data attributed to the benzylic group, $OC\underline{H}_2C_6H_5$, δ_H 4.56 ppm in C_6D_6[110] *cf.* δ_H 5.16 ppm in DMSO-d_6 (**Figure 3.20**). This kind of shift upfield is expected in aromatic solvents (*e.g.* C_6D_6, pyridine,

C_6F_6) as different chemical shifts are observed in less magnetically interactive solvents (*e.g.* CCl_4, $CDCl_3$, CD_3CN). The aromatic solvent induced shift is due to the anisotropic effect of the phenyl ring imparting increased shielding, which generally results in an upfield shift of the proton signals.

A summary of characteristic spectroscopic signals for **116**, including values from using both C_6D_6[110] and DMSO-d_6 as NMR solvents, as well as identification of a quaternary carbon signal at δ_C 112.8 ppm (previously not reported by Hashimoto[110]) is shown below (**Figure 3.20**).

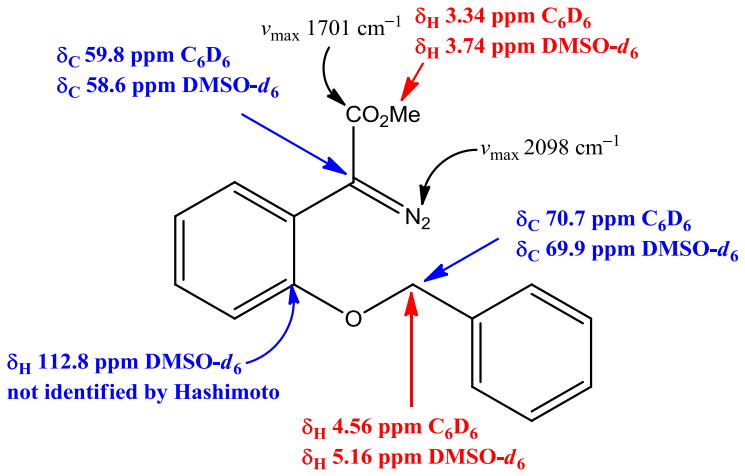
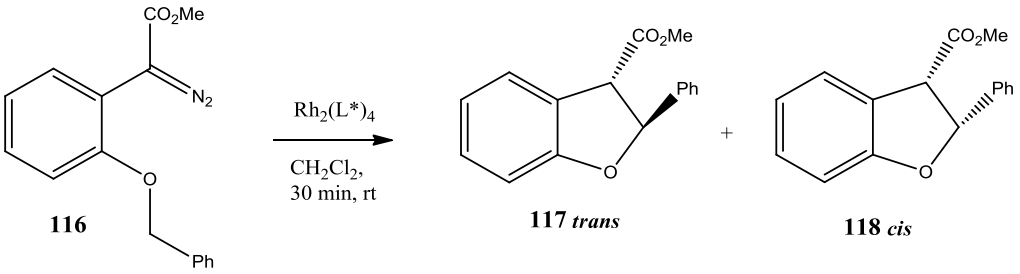


Figure 3.20: ^{1}H NMR (300 MHz, DMSO-d_6) or (270 MHz, C_6D_6)[110] and ^{13}C NMR (75.5 MHz, DMSO-d_6) or (67.8 MHz, C_6D_6)[110] values for 116

Compound **116** was used as substrate for the intramolecular C–H insertion reactions undertaken in this project since chiral stationary phase HPLC conditions were reported by Hashimoto for both corresponding *trans* and *cis* dihydrobenzofurans **117** and **118**, arising from intramolecular C–H insertion of **116**.[110]

3.3.3.3 Formation of dihydrobenzofurans using rhodium(II)-catalysed intramolecular C–H insertion

The cyclisations of α-diazoacetate **116** in this work were undertaken employing Schlenk conditions to eliminate molecular oxygen from the reaction, as previously carried out for the intermolecular cyclopropanation reactions (**Section 3.3.1.3**). While the best results obtained by Davies and Hashimoto involved using toluene and hexane as solvent under cryogenic conditions,[76,110] it was investigated whether high enantioselectivities could be obtained at ambient temperature using dichloromethane as solvent (**Scheme 3.35**).



Scheme 3.35

Cyclisation of α-diazoacetate **116** with $Rh_2(OAc)_4$ **1** was initially undertaken in dichloromethane at room temperature leading to a very low yield of a mixture of **117** and **118** (dr 73 : 27 of **117** : **118**) (**Table 3.14**, entry 1). The diastereomeric ratio was observed to 'switch' with respect to data reported by Hashimoto,[110,111] Davies[67] and Corey[112] using catalysts **13, 14, 17**[67] and **119**.[112] To the best available knowledge, cyclisation of **116** in the presence of $Rh_2(OAc)_4$ **1** has not previously been reported.

Subsequent efforts employed the enantiopure Rh_2(*S*-PTTL)$_4$ **13** and Rh_2(*S*-PTPA)$_4$ **14** catalysts to obtain comparable enantioselectivities to reported literature data,[110] under less strenuous conditions. The cyclisation of α-diazoacetate **116** in the presence of Rh_2(*S*-PTTL)$_4$ **13** was carried out at room temperature and at −60 °C using doubly distilled dichloromethane as solvent (**Table 3.14**, entries 3 and 4). As expected, almost complete diastereocontrol was observed from the reaction with isolation of the *cis* dihydrobenzofuran **118** only. After purification by column chromatography, there was a notable difference in the yield obtained for the reaction at the lower temperature (entry 4, 64% yield) compared to the reaction conducted at room temperature (entry 3, 26% yield). Interestingly, the enantioselectivities obtained for both reactions using chiral HPLC correlated excellently (92% ee at lower temperature *cf.* 93% ee for ambient temperature), which were in acceptable agreement with the literature data (**Table 3.14,** entries 3 and 4 *vs.* entry 2).[110] These results demonstrated that temperature control appeared to exert a considerable influence on the yield of the isolated product but appeared to have a minimal effect on enantioinduction.

The Rh_2(*S*-PTPA)$_4$ **14**-mediated cyclisation proceeded at room temperature with the reaction deemed to be complete after 30 min by TLC analysis and infrared spectroscopy (**Table 3.14**, entry 6). In this reaction, both diastereomers **117** and **118** were formed with a *trans/cis* ratio of 25 : 75 of **117** : **118** observed, which was in good agreement with the diastereomeric ratio reported by Hashimoto, 30 : 70 of **117** : **118** (**Table 3.14**, entry 5).[110] Column chromatography allowed clean separation of the two diastereomers which were readily distinguishable by ^{1}H NMR spectroscopic analysis, displaying a characteristic singlet at δ_H 3.21 ppm for the methyl ester group of the *cis* isomer **118** and a corresponding singlet at δ_H 3.83 ppm for the *trans* isomer **117**. Integration of the methyl ester signals in the crude ^{1}H NMR spectrum allowed determination of the diastereomeric ratio, in accordance with determination of diastereoselectivity reported by Hashimoto.[110] Other characteristic signals included two doublets at δ_H 4.29 (*J* 7.2 Hz) and δ_H 6.12 (*J* 7.2 Hz) ppm observed for the *trans*

isomer **117** and two doublets at δ_H 4.62 (*J* 10.0 Hz) and δ_H 5.99 (*J* 10.0 Hz) ppm for the *cis* isomer **118**. The stacked ^{1}H NMR spectra of **117** and **118** with illustration of characteristic signals is shown below (**Figure 3.21)**.

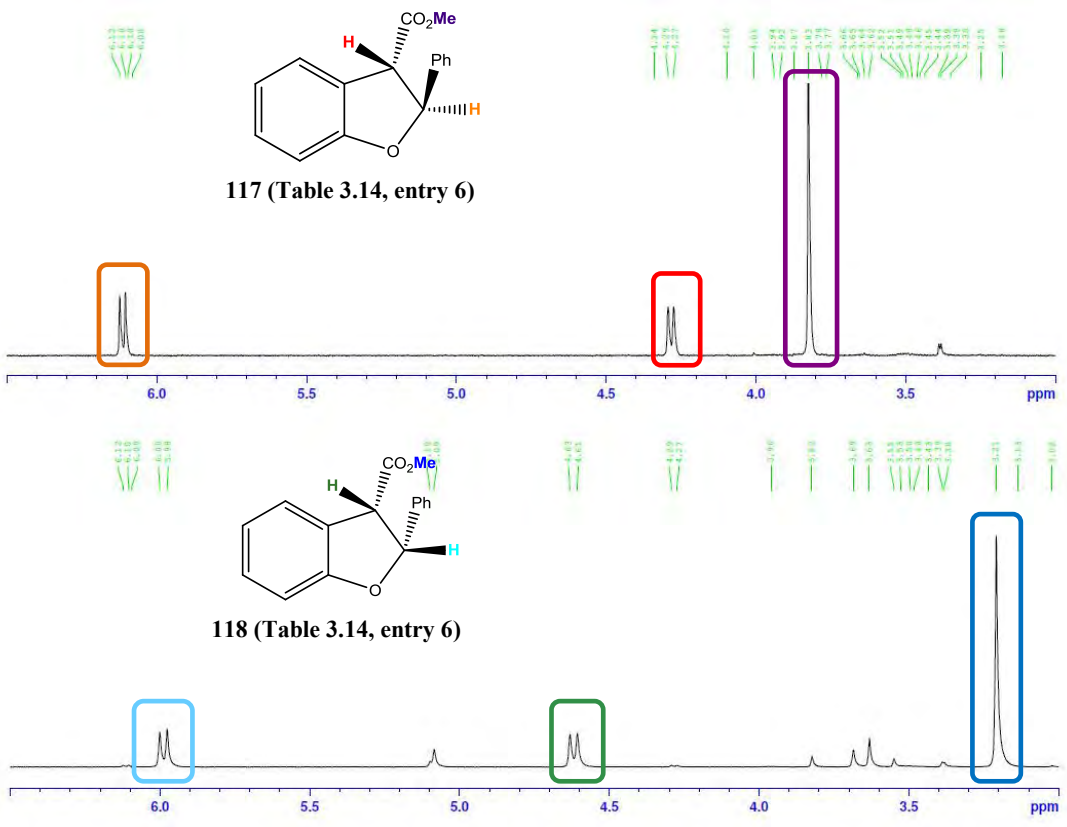


Figure 3.21: ^{1}H NMR spectra (400 MHz, $CDCl_3$) of dihydrobenzofurans 117 and 118

Analysis by chiral stationary phase HPLC was carried out using two different chiral columns, as previously described by Hashimoto.[110] Separation of the enantiomers for the *cis* dihydrobenzofuran **118** was carried out using the Chiralcel OD-H column, whereas the *trans* dihydrobenzofuran **117** was run on a Chiralpak OJ-H column. The conditions for both chiral columns are described in *Appendix IV*. The enantiopurity obtained for **118** using Rh_2(*S*-PTPA)$_4$ **14** was slightly lower than that described in the literature for the (2*R*,3*S*)-enantiomer (70% *cf.* 63% ee) (**Table 3.14**, entry 5 *vs.* 6). Curiously, the direction of enantioselection for the *trans* isomer **117** switched with respect to the literature, as the (2*S*,3*S*)-enantiomer was observed as the major enantiomer (**Table 3.14**, entry 5 *vs.* 6)[110] and the degree of enantioselectivity was also considerably reduced (80% *cf.* 8% ee, **Table 3.14**, entry 5 *vs.* 6). It should be noted that work in this project involved using dichloromethane as solvent and conducting the reaction at room temperature, while Hashimoto conducted the reaction at –60 °C using toluene as solvent, which may explain the opposite enantioinduction observed for **113** in this work.

An important aspect was that visualisation using Ultraviolet light on the TLC samples proved difficult and unreliable so to ensure better isolation, visualisation was aided through the use of phosphomolybdic acid (PMA) stain. The possible stereoisomers from this transformation and the relationship between them are illustrated below (**Figure 3.22**).

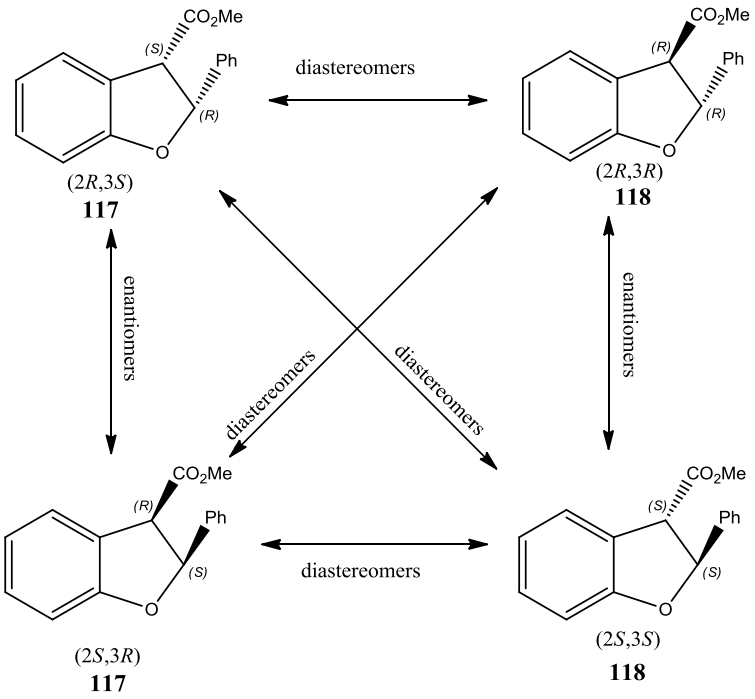


Figure 3.22: Possible stereoisomers of 117 and 118

Having established reproducibility with the literature data,[110] subsequent efforts focused on intramolecular C–H insertions involving the novel asymmetric rhodium(II) carboxylates.

The intramolecular C–H insertions employing Ford's novel rhodium(II) catalysts[48] were carried out using the same general procedure as described for the enantiopure Rh_2(*S*-PTTL)$_4$ **13** and Rh_2(*S*-PTPA)$_4$ **14** catalysts. In all cyclisations using the novel rhodium(II) carboxylates, there was formation of both *trans* and *cis* diastereomers **117** and **118**. Interestingly, the diastereomeric ratio favoured the *trans* product **117** in most cases, similar to $Rh_2(OAc)_4$ **1** but in contrast to Rh_2(*S*-PTTL)$_4$ **13** and Rh_2(*S*-PTPA)$_4$ **14** outcomes (**Table 3.12**, entries 2 and 5).[110] Separation of the diastereomers was achieved by column chromatography using ethyl acetate/hexane (5:95) for all the reactions undertaken. Analysis of the purified dihydrobenzofurans by ^{1}H NMR spectroscopy showed that the *trans* isomer **117** was isolated cleanly, however, for the *cis* isomer **118**, an azine side product **130** could not be separated from the purified product. The presence of **130** was noticeably evident from a characteristic azine band in the infrared spectrum at ν_{max} ~2111 cm^{-1}.

This azine side product **130** was noted by Hashimoto and co-workers and was observed in solvents other than toluene (ether −10 °C, dichloromethane –45 °C, hexane 23 °C), with a noticeable increase in azine formation correlating with an increase in temperature from these optimal conditions.[110] The azine **130** was also observed in the chiral HPLC traces obtained in all cases for analysis of the *cis* dihydrobenzofuran **118** employing Ford's catalysts (see *Appendix IV*, **Figure 7-9**).[48] The two peaks ascribed to the azine in the chiral HPLC traces may be due to the (*E*) and (*Z*) isomers of the azine though this is presently unconfirmed. Hashimoto *et al*. did not describe the structure of the azine product in their work,[110] so structural determination of the azine side product was not pursued in this project but is likely to be similar to the proposed structure in **Figure 3.23** below. The key signals for **130** identified in the ^{1}H NMR spectrum of **118** are three singlets at δ_H ~3.46, ~3.52 and ~3.69 ppm, as well as an apparent singlet at δ_H ~5.10 ppm ascribed to the benzylic signal and an adjacent signal of the minor isomer of **130**. It is noteworthy that for the reactions providing low isolated yields of **117** and mixed fraction **118**/**130** (**Table 3.14**), the crude ^{1}H NMR spectra were very difficult to decipher as other signals along with the characteristic signals outlined for **117**, **118** and **130** above were present.

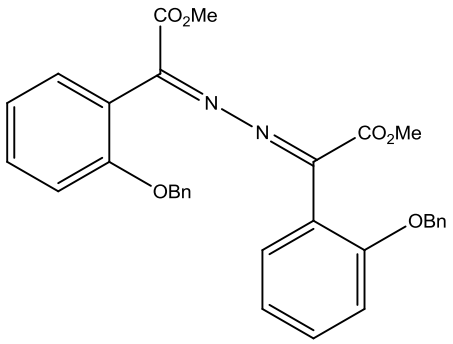
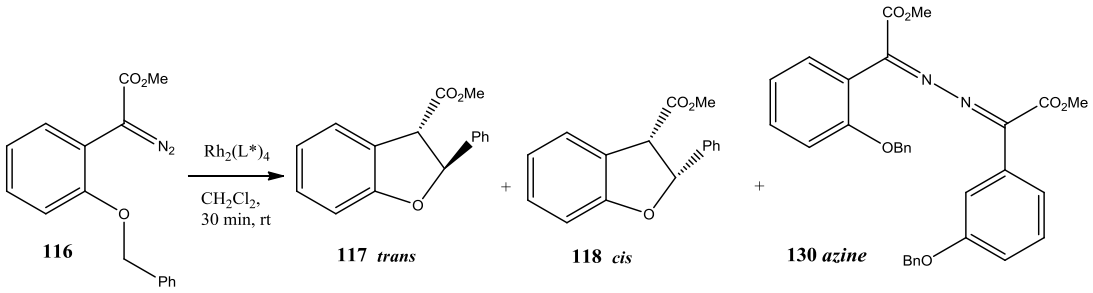


Figure 3.23: Proposed structure of azine side product 130

The diastereoselectivities, enantiopurities, combined yields and reaction conditions are summarised below (**Table 3.14**).

Table 3.14 *Rhodium(II)-catalysed intramolecular C–H insertion reactions of* **116**[a]



Entry	Catalyst	Solvent	Temp. (°C)	*trans*-117: *cis* 118[b]	Yield (%) 117	Yield (%)[c] 118+130	Ratio 118 : 130[d]	ee (%)[e,f] 117 *trans*	118 *cis*
1	$Rh_2(OAc)_4$ **1**	DCM	rt	73 : 27	10	8	1.0 : 2.26	~0[g]	
2	Rh_2(*S*-PTTL)$_4$ **13**	DCM	–45	1 : >99	–	63	–		90 (2*R*,3*S*)[110]
3	Rh_2(*S*-PTTL)$_4$ **13**	DCM	rt	1 : >99	–	26	16.0 : 1.0		92 (2*R*,3*S*)
4	Rh_2(*S*-PTTL)$_4$ **13**	DCM	–60	2 : 98	–	64	23.5 : 1.0		93 (2*R*,3*S*)
5	Rh_2(*S*-PTPA)$_4$ **14**	Toluene	–60	30 : 70	27	59	–	80 (2*R*,3*R*)	70 (2*R*,3*S*)[110]
6	Rh_2(*S*-PTPA)$_4$ **14**	DCM	rt	25 : 75	4	17	13.3 : 1.0	8 (2*S*,3*S*)	63 (2*R*,3*S*)
7	Rh_2(*R*-*p*-ClMand)$_4$ **50**	DCM	rt	68 : 32	12	7	1.97 : 1.0	65 (2*S*,3*S*)	16 (2*R*,3*S*)
8	Rh_2(*R*-*p*-MeOMand)$_4$ **51**	DCM	rt	57 : 43	30	48	4.12 : 1.0	60 (2*S*,3*S*)	23 (2*R*,3*S*)
9	Rh_2(*R*-p-MeOMand)$_4$ **51**	Toluene	rt	43 : 57	31	40	13.3 : 1.0	54 (2*S*,3*S*)[h]	6 (2*S*,3*R*)
10	Rh_2(*R*-diFMand)$_4$ **52**	DCM	rt	64 : 36	13	14	4.12 : 1.0	~0[g]	
11	Rh_2(*S*-α-Phpa)$_4$ **53**	DCM	rt	56 : 44	29	25	6.25 : 1.0	6 (2*R*,3*R*)	10 (2*S*,3*R*)
12	Rh_2('A'-MPA)$_4$ **54/55**	DCM	rt	57 : 43	19	17	7.27 : 1.0	83 (2*R*,3*R*)	54 (2*S*,3*R*)
13	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–60	82 : 18	64[i]	64[i]	–	86 (2*R*,3*R*)[j]	83 (2*S*,3*R*)[k]
14[l]	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–60	90 : 10	22	12	1.0 : 1.35	75 (2*R*,3*R*)[j]	67 (2*S*,3*R*)
15	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–78	91 : 9	96[i]	96[i]	1.0 : 2.65	86 (2*R*,3*R*)	71 (2*S*,3*R*)[k]
16	Rh_2('B'-MPA)$_4$ **54/55**	DCM	rt	33 : 67	26	25	4.26 : 1.0	77 (2*S*,3*S*)	42 (2*R*,3*S*)
17	Rh_2('B'-MPA)$_4$ **54/55**	Hexane	rt	23 : 77	12	27	3.39 : 1.0	69 (2*S*,3*S*)	48 (2*R*,3*S*)
18	Rh_2('A'-MNA)$_4$ **56/57**	DCM	rt	58 : 42	10	15	2.05 : 1.0	62 (2*R*,3*R*)[j]	27 (2*S*,3*R*)
19	Rh_2('A'-MNA)$_4$ **56/57**	Toluene	rt	80 : 20	41	36	3.96 : 1.0	58 (2*R*,3*R*)[h]	45 (2*S*,3*R*)
20	Rh_2('B'-MNA)$_4$ **56/57**	DCM	rt	56 : 44	9	23	3.15 : 1.0	11 (2*R*,3*R*)[j]	~0[g]
21	Rh_2('B'-MNA)$_4$ **56/57**	DCM	rt	56 : 44	9	23	3.15 : 1.0	44 (2*R*,3*R*)[k]	~0[g]
22	Rh_2('B'-MBrPA)$_4$ **58/59**	DCM	rt	50 : 50	6	14	1.69 : 1.0	70 (2*S*,3*S*)[j]	50 (2*R*,3*S*)
23	Rh_2('A'-BBrPA)$_4$ **60/61**	DCM	rt	36 : 64	3	7	4.70 : 1.0	72 (2*S*,3*S*)[j]	42 (2*R*,3*S*)
24	Rh_2('A'-BBrPA)$_4$ **60/61**	Toluene	rt	66 : 34	42	29	7.40 : 1.0	68 (2*R*,3*R*)[h]	42 (2*S*,3*R*)[k]

[a] Reactions conducted using the general procedure for rhodium-mediated intramolecular C–H insertion reactions.

[b] Ratios based on integration of the methyl ester (CO_2CH_3) signals from the ^{1}H NMR spectra of the crude products.

[c] Combined yield of **118** and **130** following column chromatography. While **117** can be separated, **118** and **130** are isolated as a combined fraction.

[d] Ratios based on integration of assumed benzylic signals for *cis* and *trans* azine **130** at δ_H ~5.09 ppm and signal for **118** at δ_H 5.99 ppm (ArH) in the ^{1}H NMR spectrum of the purified mixed fraction of **118** and **130.**

[e] Determined by chiral stationary phase HPLC on material **117** and **118** obtained after chromatography (see *Appendix IV* for details).

[f] Entries 2 and 5 refer to literature data.[110] Assignment of stereochemistry of the products is by comparison with previously reported data.[110]

[g] Where enantiomeric excess was ≤ 5% the sample was regarded as achiral.

[h] In retrospect, samples used for chiral HPLC analysis were too concentrated and as a result the % ee is likely to be underestimated.

[i] Samples of **117** and **118/130** not isolated and corresponds to the overall yield of purified mixed fraction **117/118/130**.

[j] Enantiopurity is based on integration of peaks for **117** using Chiralcel OD-H column. Earlier work has helped distinguish between the enantiomers for **117**; t_R 5.1 min (2*R*,3*R*) and t_R 6.2 min (2*S*,3*S*).

[k] Signals on the HPLC not fully resolved and therefore, enantiopurities are estimated rather than exact.

[l] Reaction carried out on a larger scale than usual (× 3.8 times usual scale) to provide samples for optical rotation analysis.

Isolated yields of both diastereomers **117** and **118** ranged from moderate to good and the combined yield of the isolated products and the azine side product are included in **Table 3.14**. The results obtained using chiral HPLC analysis showed that many of the catalysts conferred lower enantioselectivities for the *cis* isomer **118** than for the *trans* isomer **117**, in contrast to the reports by Davies[67] and Hashimoto[110] of high ee's for the *cis* isomer **118**.

Overall, an interesting trend is observed, in terms of the efficiency of the C–H insertion process using the novel chiral rhodium(II) carboxylates. Clearly, reaction with $Rh_2(OAc)_4$ at room temperature using dichloromethane as solvent is very poorly efficient in terms of C–H insertion. Both this work and earlier reports by Davies and Hashimoto have shown increased efficiency in C–H insertions at lower reaction temperatures (**Table 3.14**, entries 3, 4 and 5). Significantly, using the modified chiral catalysts *e.g.* Rh_2(*R*-*p*-MeOMand)$_4$ **51** (**Table 3.14**, entries 8 and 9), Rh_2('A'-MNA)$_4$ **56/57** and Rh_2('A'-BBrPA)$_4$ **60/61** (**Table 3.14**, entries 19 and 24), C–H insertion is proceeding very efficiently even at room temperature, particularly for reactions using toluene as solvent.

While the degree of enantiocontrol for the *cis* isomer **118** was low for a number of the catalysts, ranging from 6–23% ee, the menthol- and borneol-derived catalysts displayed modest enantioinduction for the *cis* dihydrobenzofuran **118**, with enantiopurities ranging from 27–67% ee (**Table 3.14**, entries 12–23). Results for the *trans* diastereomer **117** were more encouraging, with good to high enantioselectivities (58–83% ee) achieved in nearly all cases. Asymmetric induction obtained using Rh_2('A'-MPA)$_4$ **54/55**, Rh_2('B'-MPA)$_4$ **54/55** and Rh_2('A'-MNA)$_4$ **56/57** catalysts proved particularly impressive (**Table 3.14**, entries 12, 13, 15, 16 and 18).

On varying reaction parameters such as choice of solvent and temperature of the reaction, some interesting results for enantioselectivity and diastereomeric excess were observed. A solvent effect illustrated a decrease in enantioselectivity for **117** and **118** (**Table 3.14**, entry 8 *vs.* 9) while in two cases (**Table 3.14**, entries 19 *vs.* 18 and 17 *vs.* 16), a decrease in enantiomeric excess was observed for *trans* isomer **117** accompanied by an increase in enantiopurity for the *cis* isomer **118**, albeit with modest differences. An increase in diastereomeric excess was identified through variation of solvent (**Table 3.14**, entry 19 *vs.* 18) and interestingly, on changing the solvent from dichloromethane to toluene (**Table 3.14**, entry 23 *vs.* 24), complete inversion of diastereoselectivity and direction of enantioselectivity was observed for both *trans* and *cis* dihydrobenzofurans **117** and **118**. This is the only example in this study using Ford's catalysts where solvent choice was observed as a deciding factor in determining which enantiomeric direction was favoured, as well as direction of diastereomeric excess. A temperature effect highlighted an increase in isolated yields of **117** and **118** on carrying out the reaction at lower temperature (**Table 3.14**, entry 15 *vs.* 13) which was in good agreement with earlier work (**Table 3.14**, entry 3 *vs.* 4).

The enantiomeric excess (83% ee) obtained for the *trans* dihydrobenzofuran **117** using Rh_2('A'-MPA)$_4$ **54/55** (**Table 3.14**, entry 12) represents the highest value to date for the *trans* substrate using the intramolecular C–H insertion approach. Hashimoto had previously obtained 80% ee using Rh_2(*S*-PTPA)$_4$ **14** in toluene at –60 °C,[110] but this was the minor diastereomeric component in comparison to the isolation of **117** as the major product in both diastereo- and high enantiomeric excess in this work. Further optimisation applying Hashimoto's conditions with the best performing catalyst from this work were subsequently carried out (**Table 3.14**, entries 13 and 15). There was a minor increase (86% *cf.* 83% ee, see **Table 3.14** footnote [j]) for the *trans* diastereomer **117** and a significant increase in enantioselectivity (83% *cf.* 54% ee, see **Table 3.14** footnote [k]) was observed in the case of *cis* dihydrobenzofuran **118** (**Table 3.14**, entry 13 *vs.* 12). On further lowering the temperature to –78 °C, no enhancement in enantioselectivity was observed for the *trans* isomer **117** (86% ee), although a decrease in enantiopurity was obtained for the *cis* isomer **118** (71% *cf.* 83% ee, see footnote [k]) (**Table 3.14**, entry 15 *vs.*12).

This illustrates that using these optimised conditions, high enantioselectivities for both *trans* and *cis* diastereomers **117** and **118** were successfully achieved employing the novel rhodium(II) catalysts. A trend graph comparing the enantioselectivities for *trans* and *cis* isomers **117** and **118** is shown below (**Figure 3.24** and **Figure 3.25**).

Comparison of enantioselectivities for trans *dihydrobenzofuran* **117** *from rhodium(II)-catalysed C–H insertion reactions of* **116**

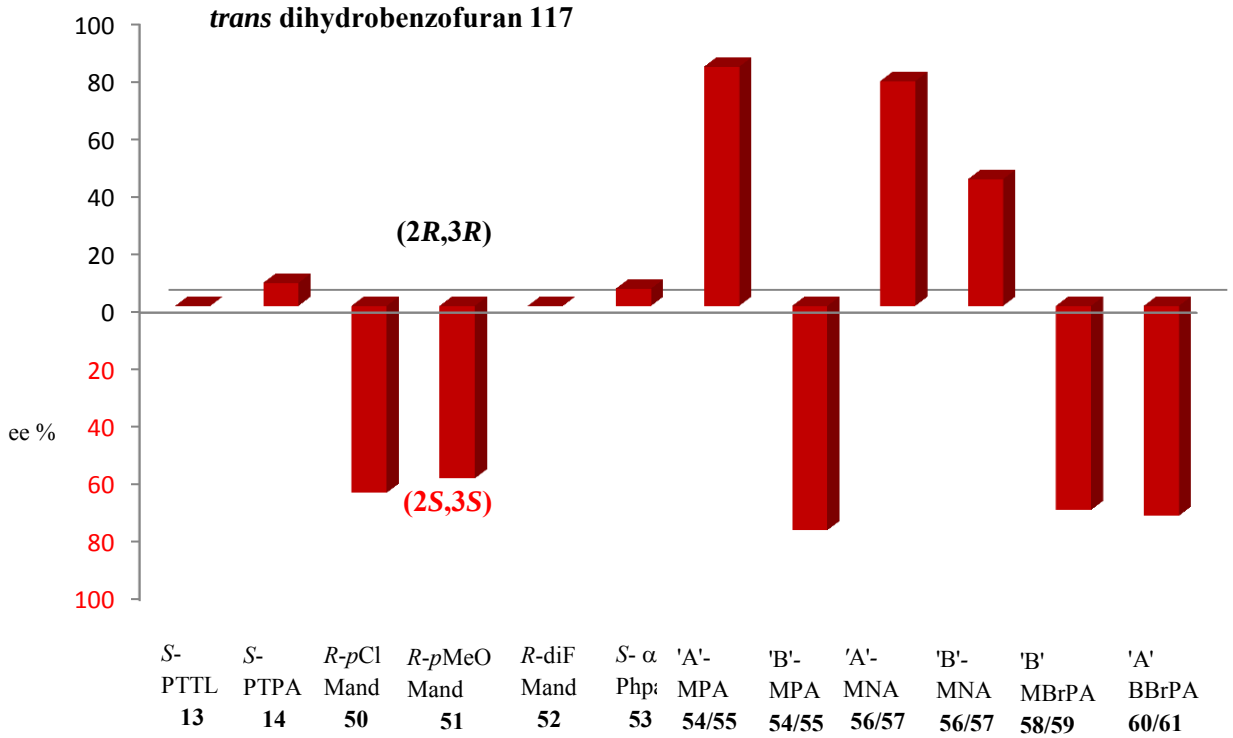


Figure 3.24

Comparison of enantioselectivities for cis *dihydrobenzofuran* **118** *from rhodium(II) -catalysed C–H insertion reactions of* **116**

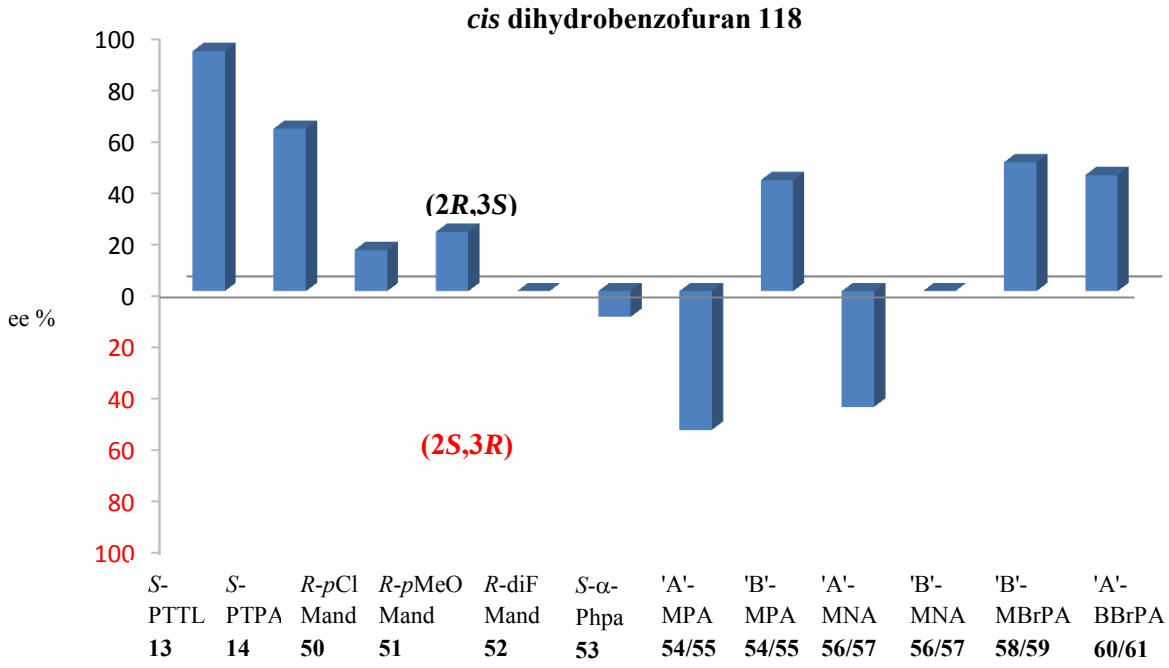


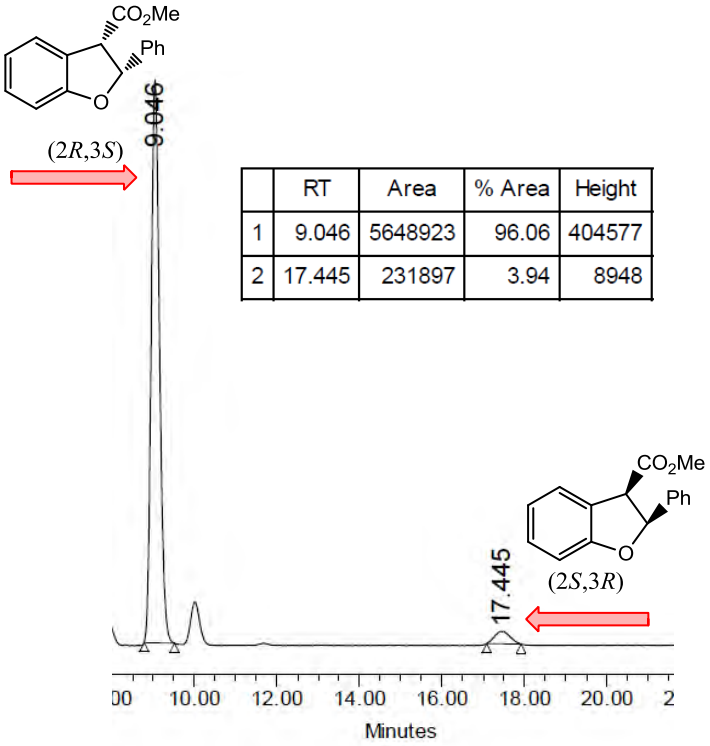
Figure 3.25

In addition, optical rotation analysis was carried out on the *trans* and *cis* dihydrobenzofurans **117** and **118** to ensure that they were in reasonable agreement with data reported by Hashimoto and co-workers.[110] This was carried out on sample obtained in **Table 3.14**, entry 14, with the reaction conducted on a larger scale than normal (3.8 times scale of the standard reaction) to provide samples for optical rotation analysis. Using the same concentrations and solvent as described by Hashimoto,[110] the directions were in agreement with the literature while the absolute values obtained were lower. These results are summarised below (**Table 3.15**).

Table 3.15

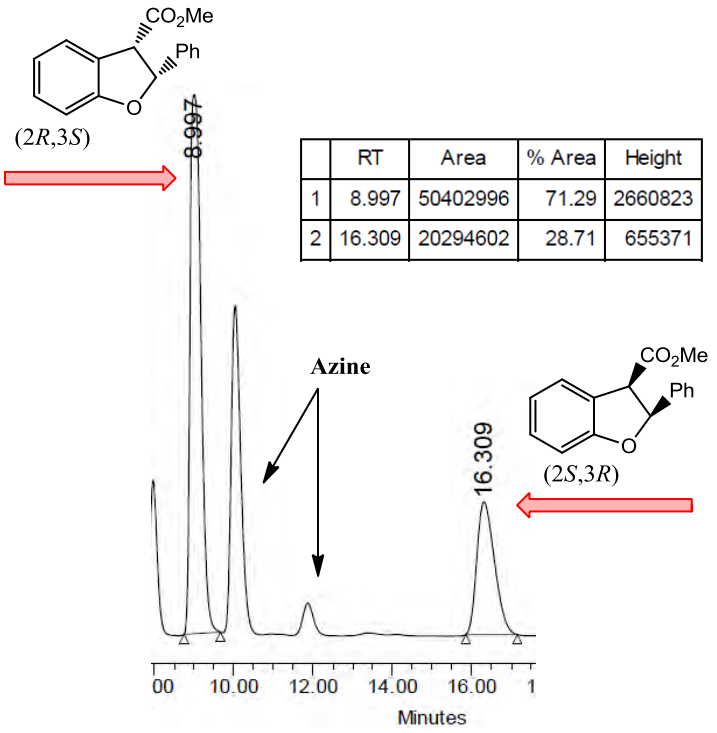
Entry	Compound	Rotation	ee (%)
1	**117**	$[\alpha]_D^{21}$ −58.2[110]	80[110]
2	**117**	$[\alpha]_D^{20}$ −39.1	75
3	**118**	$[\alpha]_D^{21}$ +57.9[110]	70[110]
4	**118**	$[\alpha]_D^{20}$ +29.4	67

The HPLC traces obtained for both *trans* and *cis* dihydrobenzofurans **117** and **118** are shown below (**Figure 3.26–3.29**). The HPLC traces for the *trans* isomer **117**, (**Figure 3.28** and **Figure 3.29**), involving Rh_2('A'-MPA)$_4$ **54/55** and Rh_2('B'-MPA)$_4$ **54/55** clearly illustrate the inversion of enantiocontrol through the use of the (*S*-) and (*R*-)/'A' and 'B' form of the catalyst (**Table 3.14**, entry 12 *vs.* 16).



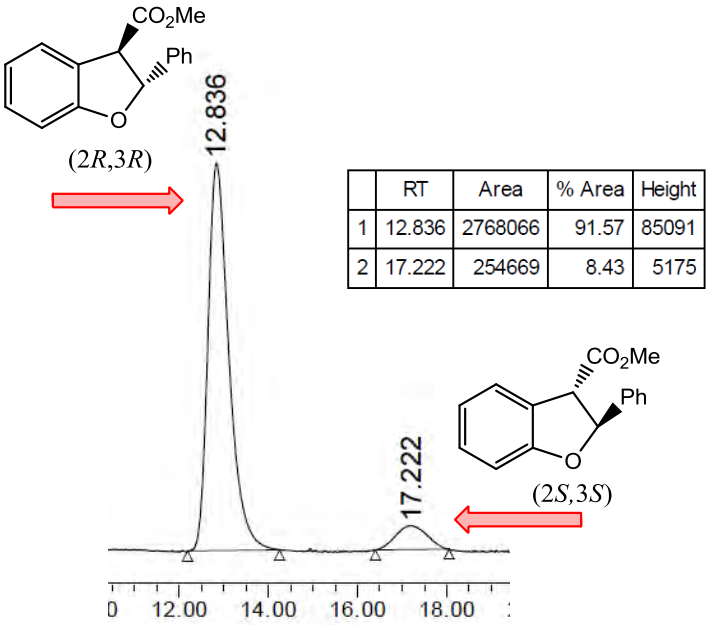
	RT	Area	% Area	Height
1	9.046	5648923	96.06	404577
2	17.445	231897	3.94	8948

Figure 3.26: *Cis* dihydrobenzfuran 118 (92% ee) from Rh_2(S-PTTL)$_4$-catalysed cyclisation(Table 3.13, entry 3)



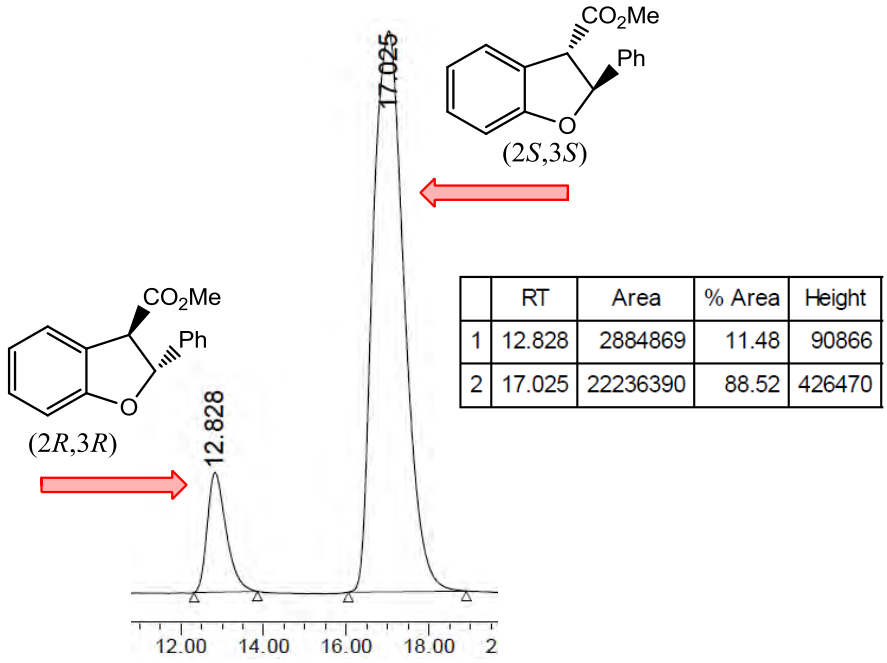
	RT	Area	% Area	Height
1	8.997	50402996	71.29	2660823
2	16.309	20294602	28.71	655371

Figure 3.27: *Cis* dihydrobenzofuran 118 (42% ee) from Rh_2('B'-MPA)$_4$-catalysed cyclisation (Table 3.13, entry 16)



	RT	Area	% Area	Height
1	12.836	2768066	91.57	85091
2	17.222	254669	8.43	5175

Figure 3.28: *Trans* dihydrobenzofuran 117 (83% ee) from Rh_2('A'-MPA)$_4$-catalysed cyclisation (Table 3.13, entry 12)



	RT	Area	% Area	Height
1	12.828	2884869	11.48	90866
2	17.025	22236390	88.52	426470

Figure 3.29: *Trans* dihydrobenzofuran 117 (77% ee) from Rh_2('B'-MPA)$_4$-catalysed cyclisation (Table 3.13, entry 16)

As Hashimoto ran chiral stationary phase HPLC for *trans* and *cis* dihydrobenzofurans **117** and **118** using separate columns,[110] the majority of the analysis for this work was carried out on two different columns following Hashimoto's data leading to the enantiopurities summarised in **Table 3.14** other than those labelled footnote *j*.

However, later in this study it was noted the enantiopurities of both **117** and **118** can be determined on a single injection on Chiralcel OD-H column using the conditions previously employed in this work (see *Appendix IV*). The samples used for this mixed injection were the purified *trans* isomer **117** (from reaction **Table 3.14**, entry 8) and the purified *cis* isomer **118** (from reaction **Table 3.14**, entry 5). Using separate injections initially and by comparison of enantiopurities previously reported in **Table 3.14** (entries 8 and 5), the enantiomers for both **117** and **118** could be readily identified. The peaks for the *trans* diastereomer **117** were located at t_R 5.1 min (2*R*,3*R*) and 6.2 min (2*S*,3*S*), while the peaks for the *cis* diastereomer **118** were observed at t_R 8.2 min (2*R*,3*S*) and 17.3 min (2*S*,3*R*). Following this, a mixed injection containing both *trans* and *cis* isomers **117** and **118** was carried out on the Chiralcel OD-H column and it was observed that the peaks corresponding to the four enantiomers could be separated and identified on a single HPLC trace (**Figure 3.30**).

This observation is likely to facilitate efficient analysis for future investigations. The chiral HPLC trace for the mixed injection, as well as the individual *trans* and *cis* isomers run on the Chiralcel OD-H column are shown below (**Figure 3.30**).

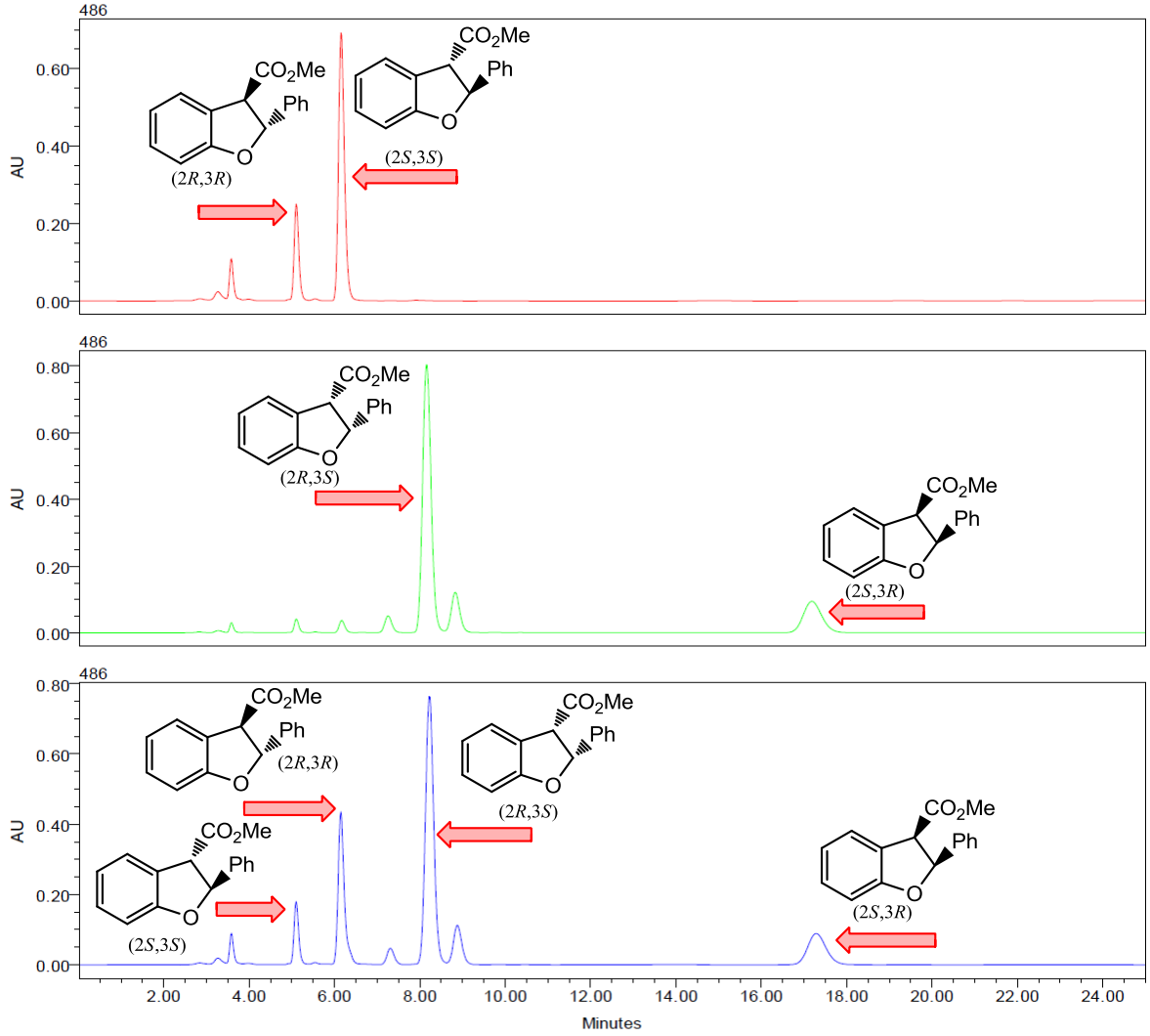


Figure 3.30: **Individual and mixed samples of 117 and 118 run on Chiralcel OD-H using conditions outlined in *Appendix IV* (Table 2)**

In certain cases, enantiopurities obtained for the *trans* isomer **117** were estimated rather than exact, due to the sample being too concentrated or incomplete resolution of peaks (**Table 3.14**, entries 13, 14, 18, 20, 22 and 23). In the ^{1}H NMR analysis of the *cis* isomer **118**, on occasion, the *trans* isomer **117** co-eluted with the **118** and this was also observed in the chiral stationary phase HPLC run on the Chiralcel OD-H column. Through the mixed injection work above, the signals ascribed to the (2*R*,3*R*)- and (2*S*,3*S*)-enantiomers could be identified for samples run on the Chiralcel OD-H column. This allowed accurate determination of the enantiopurities for the *trans* dihydrobenzofuran **117** (**Table 3.14**, entries 13, 14, 18, 20, 22 and 23), which were generally consistent with the estimated enantioselectivities (see *Appendix IV*, **Figure 5** and **Figure 6**).

In summary, through a combination of chiral HPLC approaches, accurate enantiopurity data have been determined in most instances. Only the samples in **Table 3.14** labelled with footnote *k* remain as estimated and warrant further investigation.

3.4 Conclusions

- In the course of this work, several novel asymmetric rhodium(II) catalysts were screened on two substrates applicable for intermolecular cyclopropanation and intramolecular C–H insertion. The proposed screening for the intramolecular cyclopropantion did not proceed due to difficulty in cleanly forming and isolating the desired products.

- The novel rhodium(II) catalysts provided low enantiomeric excess for the cyclopropanation systems. However, high enantiopurities were obtained for the C–H insertions series. The most successful examples of high asymmetric induction involved the *trans* dihydrobenzofuran **117** using Rh_2('A'-MPA)$_4$ **54/55** and Rh_2('B'-MPA)$_4$ **54/55** catalysts.

- Highly stereoselective intramolecular C–H insertions were achieved using Ford's novel rhodium(II) catalysts (up to 86% ee) for the *trans* isomer **117**. This is the highest enantiopurity reported for **117** obtained solely *via* carbenoid-mediated intramolecular C–H insertion, demonstrating that these newly-developed catalysts can be highly enantioselective.

- In this work, efficient asymmetric C–H insertion was attained using less strenuous conditions than previously reported. Interestingly, the diastereomeric ratio favoured generation of *trans* isomer **117** in most cases in this work, as well as providing high enantiopurities for **117**. These results were in contrast to reports of Hashimoto,[110,111] Davies[67] and Corey[112] which previously disclosed predominant formation of *cis* isomer **118** and formation of **117** as a minor component in low dr.

- **Figure 3.31** illustrates the overall trends of the enantiopurities obtained for the successful intermolecular cyclopropanation and intramolecular C–H insertion reactions using the novel rhodium(II) carboxylates.

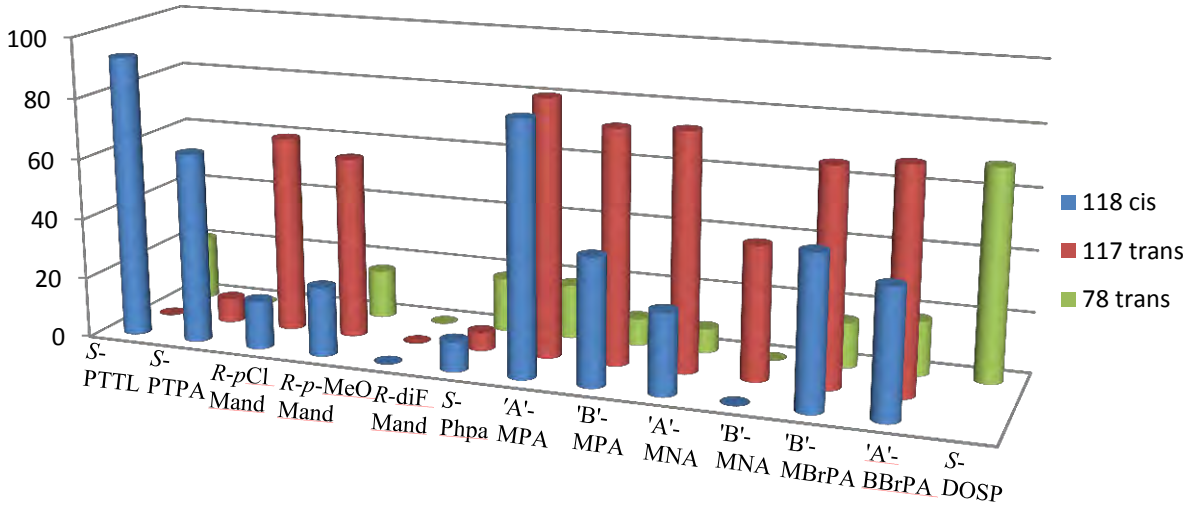


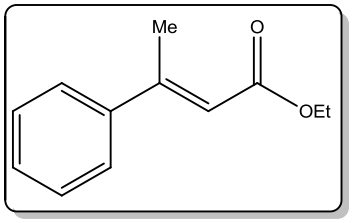
Figure 3.31

3.5 General procedures and Experimental

The general procedures are the same as those described previously (**Section 2.6**).

Synthesis of esters and alcohols

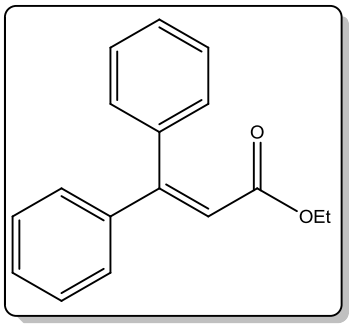
(*E*)-Ethyl 3-phenylbut-2-enoate 94[95]



A suspension of sodium hydride (1.65 g, 60% mineral dispersion, 68.7 mmol) in tetrahydrofuran (50 mL) was cooled to 0 °C and neat triethyl phosphonoacetate (9.2 mL, 73.4 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C and then a solution of acetophenone (5.50 g, 45.8 mmol) in tetrahydrofuran (20 mL) was added dropwise to the reaction mixture at 0 °C for 1.5 h. The reaction was quenched by addition of aqueous saturated ammonium chloride (30 mL) followed by separation of the layers and extraction of the aqueous layer with ether (3 × 60 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated *in vacuo* to give the crude *ester* as a pale yellow oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (1:99), (5:95), (10:90) afforded the purified *ester* **94** (4.74 g, 59%)* as a yellow oil; ν_{max}/cm^{-1} (film) 2980, 2956, 2927, 1714, 1629, 1578, 1495, 1447, 1378, 1366, 1344, 1273, 1172, 1044, 872, 767, 695; δ_H (400 MHz, $CDCl_3$) 1.31 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 2.58 [3H, s, $CHCC\underline{H}_3$], 4.21 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.13 [1H, s with unresolved coupling, *J* 1.2, $C\underline{H}CCH_3$], 7.30–7.52 [5H, m, 5 × aromatic $\underline{H}$]. Spectral properties were consistent with reported data.[95]

* Assigned as (*E*) isomer **94** by comparison with ^{1}H NMR signals described for **94** and corresponding (*Z*) isomer at δ_H 5.89 ppm by Maleczka.[95]

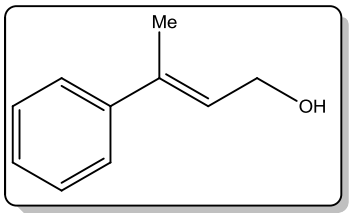
Ethyl 3,3-diphenylacrylate 95[122]



This was prepared following the procedure for **94**, from sodium hydride (1.19 g, 60% mineral dispersion, 49.4 mmol) dissolved in tetrahydrofuran (60 mL), triethyl phosphonoacetate (6.6 mL, 52.77 mmol), a solution of benzophenone (6.00 g, 32.9 mmol) in tetrahydrofuran (30 mL) to give the crude *ester* as a viscous pale oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) furnished the purified *ester* **95** (7.19 g, 86%)* as a yellow oil; ν_{max}/cm^{-1} (film) 2928, 1721, 1699, 1660, 1618, 1599, 1578, 1492, 1446, 1367, 1318, 1277, 1153, 698; δ_H (400 MHz, $CDCl_3$) 1.10 [3H, t, *J* 7.2, $CH_2C\underline{H}_3$], 4.05 [2H, q, *J* 7.2, $C\underline{H}_2CH_3$], 6.36 [1H, s, $C\underline{H}CO_2Et$], 7.18–7.40 [10H, m, 10 × aromatic <u>H</u>]. Spectral characteristics were consistent with previously reported data.[122]

* Integration of the aromatic protons was higher than expected presumably due to unreacted benzophenone (~50 mol%). Additional evidence for presence of benzophenone was observed in the infrared spectrum of **95**; ν_{max} 1660 cm^{-1}.

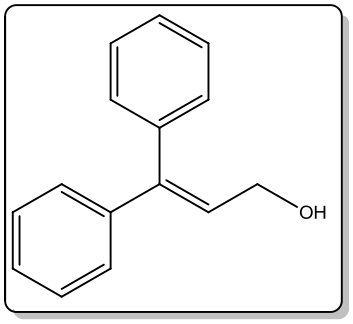
(*E*)-3-Phenylbut-2-en-1-ol 92[95,96]



A solution of ester **94** (4.14 g, 21.8 mmol) in ether (50 mL) was stirred at 0 °C for 5 min. A solution of diisobutylaluminium hydride (DIBAl-H) (1.0 M in hexanes, 47.9 mL, 47.90 mmol) was added slowly over 20 min to the reaction mixture. The reaction mixture was gradually warmed to room temperature overnight and subsequently cooled to 0 °C. The reaction was quenched by slow addition of water (50 mL) and brine (30 mL). A white solid material was observed and this was dissolved by addition of aqueous hydrochloric acid (3.2 M, 60 mL) and two layers were now clearly visible. Separation of the layers was followed by extraction of the aqueous layer with ether (3 × 60 mL) and the combined organic extracts were dried over magnesium sulfate followed by concentration under reduced pressure to provide the crude *alcohol* as a pale oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80) followed by (40:60) yielded the pure *alcohol* **92** (3.13 g, 97%)* as a light yellow oil; ν_{max}/cm^{-1} (film) 3327, 2923, 1648, 1494, 1445, 1380, 1112, 1065, 1001, 757, 696; δ_H (400 MHz, $CDCl_3$) 2.08 [3H, s, $C\underline{H}_3$], 4.36 [2H, d, *J* 6.8, $C\underline{H}_2OH$], 5.97 [1H, t with further unresolved splitting, *J* 6.4, $C\underline{H}CH_2OH$], 7.21–7.44 [5H, m, 5 × aromatic <u>H</u>]. Spectral properties were consistent with previously reported data.[95,96]

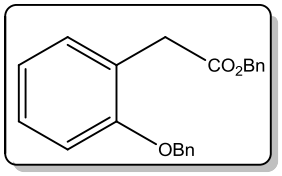
* Assigned as (*E*) isomer **92** by comparison with ^{1}H NMR signals for **92** in the literature[95,96] and ^{1}H NMR signals for the corresponding (*Z*) isomer at δ_H 5.72 ppm described by Mantilli.[97]

3,3-Diphenylprop-2-en-1-ol 93[122,123]



This was prepared following the procedure described for **92**, from ethyl 3,3-diphenylacrylate **95** (impure sample containing ~50 mol% benzophenone) (4.50 g, 17.84 mmol estimated to contain ~9 mmol **95**) dissolved in ether (50 mL) and DIBAl-H (1.0 M in hexanes, 39.3 mL, 39.30 mmol). Removal of solvent under reduced pressure yielded the crude *alcohol* as a viscous pale oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (15:85) to (20:80) provided the pure *alcohol* **93** (2.03 g, 54% estimated based on impure sample, quantitative yield based on ~9 mmol **95** present) as a pale yellow oil which later solidified upon storage to give a white solid; ν_{max}/cm^{-1} (film) 3358, 2914, 1444; δ_H (300 MHz, $CDCl_3$) 1.40 [1H, br s, O<u>H</u>], 4.23 [2H, dd, *J* 6.6, 4.2, C<u>H</u>$_2$OH], 6.25 [1H, t, *J* 6.9, C<u>H</u>CH$_2$OH], 7.10–7.41 [10H, m, 10 × aromatic <u>H</u>]. Spectral properties were consistent with previously reported data.[122,123]

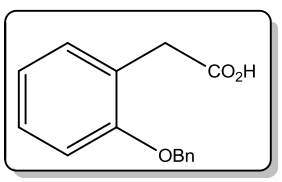
1-(Benzyloxy)-2-[(benzyloxy)methyl]benzene 127[48,120]



Anhydrous potassium carbonate (10.60 g, 77.0 mmol) was added in one portion to a stirring solution of 2-(2-hydroxyphenyl)acetic acid (5.00 g, 33.0 mmol) in dimethylformamide (75 mL) at room temperature. Neat benzyl bromide (7.8 mL, 66.0 mmol) was added dropwise to the reaction mixture followed by stirring at room temperature for 24 h. The progress of the reaction was monitored by TLC analysis and was found to be complete after 24 h. The reaction mixture was diluted with ether (100 mL) and water (50 mL), followed by gradual addition of aqueous hydrochloric acid (2.0 M, 2 × 75 mL). The layers were separated and the aqueous layer was extracted using ether (3 × 50 mL). The combined organic extracts were washed with aqueous hydrochloric acid (2.0 M, 2 × 75 mL), dried using magnesium sulfate and concentrated under reduced pressure to give the crude dibenzylated ester as a pale pink solid. The crude product was washed with ice-cold hexane (~50 mL) and dried using vacuum filtration to give the purified *dibenzylated ester* **127** (9.02 g, 82%) as a pale pink solid; ν_{max}/cm^{-1} (KBr) 3034, 2914, 1737, 1603, 1497, 1453, 1379, 1247, 1150; δ_H (400 MHz, $CDCl_3$)* 3.74 [2H, s, C<u>H</u>$_2$CO$_2$CH$_2$C$_6$H$_5$], 5.05 [2H, s, one of OC<u>H</u>$_2$C$_6$H$_5$], 5.09 [2H, s, one of OC<u>H</u>$_2$C$_6$H$_5$], 6.93 [2H, t, *J* 7.6, 2 × aromatic <u>H</u>], 7.19–7.40 [12H, m, 12 × aromatic <u>H</u>]**. Spectral properties were consistent with previously reported data.[120]

* Spectrum contains residual DMF.
** Integration is slightly higher than expected due to overlap with $CDCl_3$.

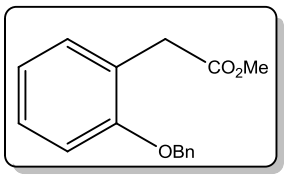
2-[2-(Benzyloxy)phenyl]acetic acid 128[48,121]



Dibenzylated ester **127** (7.90 g, 23.70 mmol) was added portionwise to a stirring mixture of tetrahydrofuran/methanol/water (150 mL/ 50 mL/ 50 mL) at room temperature. Anhydrous lithium hydroxide (5.70 g, 237 mmol) was added in one portion to the reaction mixture followed by stirring overnight at room temperature. Reaction progress was monitored using TLC analysis and was found to be complete after overnight stirring. The

reaction mixture was cooled to 0 °C and conc. hydrochloric acid (25 mL) was slowly added until the mixture was acidic as determined by litmus paper. The reaction mixture was diluted with brine (30 mL) and ether (50 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and concentrated *in vacuo* to afford the crude *monobenzylated acid* as a yellow oil. The residue was diluted in ether (30 mL) and extracted with aqueous sodium hydroxide (1.0 M, 2 × 50 mL). The combined aqueous extracts were washed with ether (30 mL), acidified with aqueous hydrochloric acid (3.2 M, ~25 mL) and extracted with ether (2 × 50 mL). The combined organic extracts were dried using magnesium sulfate and excess solvent removed *in vacuo* to give the *monobenzylated acid* **128** (4.02 g, 70%) as a white solid; ν_{max}/cm^{-1} (film) 3100–2600 (COOH), 3033, 1708, 1604, 1497, 1453, 1407, 1291, 1246, 1114, 1024, 752; δ_H (400 MHz, $CDCl_3$) 3.71 [2H, s, $C\underline{H}_2CO_2H$], 5.07 [2H, s, $OC\underline{H}_2C_6H_5$], 6.94 [2H, t with further unresolved splitting, *J* 7.6, 2 × aromatic <u>H</u>], 7.18–7.41 [7H, m, 7 × aromatic <u>H</u>]. Spectral properties were consistent with previously reported data.[121]

Methyl 2-[2-(benzyloxy)phenyl]acetate 129[48,121]

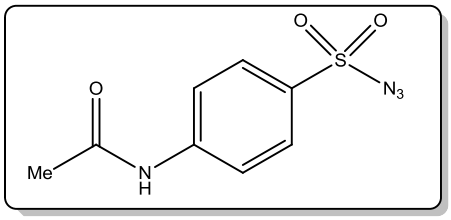


Conc. sulfuric acid (1 mL) was added to a stirring solution of acid **128** (4.70 g, 19.39 mmol) in methanol (50 mL) and the reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled to room temperature followed by addition of anhydrous sodium bicarbonate (1.5 g). The mixture was filtered and concentrated under reduced pressure to afford the crude *monobenzylated methyl ester* **129** (4.65 g, quantitative yield) as a viscous pale yellow oil; ν_{max}/cm^{-1} (film) 3033, 2950, 1736, 1603, 1590, 1498, 1453, 1382, 1342, 1291, 1248, 1159, 1113, 1016, 753, 697; δ_H (400 MHz, $CDCl_3$)* 3.63 [3H, s, $CO_2C\underline{H}_3$], 3.68 [2H, s, $C\underline{H}_2CO_2CH_3$], 5.07 [2H, s, $OC\underline{H}_2C_6H_5$], 6.93 [2H, t, *J* 8.4, 2 × aromatic <u>H</u>], 7.16–7.43 [7H, m, 7 × aromatic <u>H</u>]. Spectral properties were consistent with previously reported data.[121]

* Sample contains methanol.

Preparation of α-diazoacetates

***p*-Acetamidobenzenesulfonyl azide (*p*-ABSA) 77**[124]

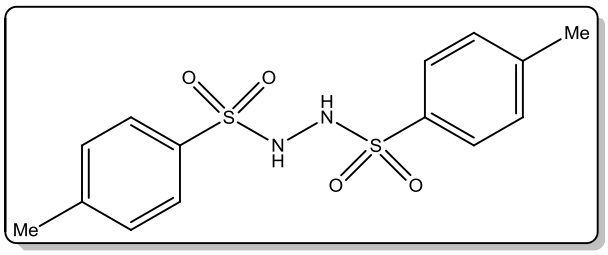


p-Acetamidobenzenesulfonyl chloride (50.00 g, 210 mmol) was dissolved in acetone (400 mL) and placed in a 2 L conical flask while stirring at room temperature. Sodium azide (16.60 g, 250 mmol) was weighed out in the fumehood, dissolved in water (120 mL) and decanted slowly into the conical flask with the reaction stirred at room temperature for 24 h and the conical flask covered by a clock glass. An orange colour was observed at this point. After stirring for 24 h, the reaction mixture was poured onto water (1.5 L) and a pink/salmon colour was now observed. This was then stirred for 4 h at room temperature with a gradual precipitation of the product observed. The solid was isolated by vacuum filtration and subsequently dried in a desiccator using potassium hydroxide as drying agent for 5 days to give the crude *azide* **77** (45.1 g, 90%) as a pale pink solid.

Caution! *Sodium azide is toxic and explosive. The weighing of this should be conducted in a well-ventilated fumehood.*

Note: The aqueous filtrate in the workup contains some excess azide and this must be quenched using the following procedure.[125] *Approximately ~7 mL of a (20%, w/w) aqueous solution of sodium nitrite per gram of sodium azide used is added with stirring. An aqueous sulphuric acid solution (20%, v/v) is added until the reaction mixture is classed as acidic on turning blue litmus paper red. Once no more nitrogen is given off the acidified solution is tested with starch iodide which turns blue meaning the decomposition of the excess sodium azide is complete before disposal. The order of addition is essential, as addition of the acid before the nitrite will result in the evolution of hydrazoic acid (HN_3) which is a poisonous and highly explosive gas.*

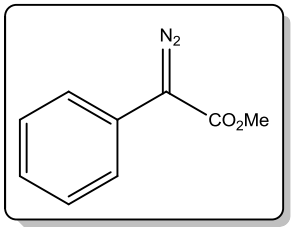
N,N'-Ditosylhydrazine 96[94]



Experimental procedure and spectroscopic properties for **96** are identical to those described earlier in this work (see p 297).

Methyl 2-diazo-2-phenylacetate 76[48,126]

Method A: Ford's optimised conditions[48]



Methyl 2-phenylacetate (2.81 g, 19.98 mmol) and 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (4.5 mL, 29.97 mmol) were dissolved in distilled acetonitrile (30 mL) and the reaction mixture was stirred at 40 °C. A solution of *p*-ABSA **77** (5.28 g, 21.98 mmol and additional 3 × 0.1 equiv. 2.2 mmol) in distilled acetonitrile (50 mL) was added dropwise and the reaction mixture was stirred at 40 °C. The reaction progress was monitored by TLC analysis and after stirring for 2 h at 40 °C, the reaction appeared to be complete. Evaporation of solvent furnished the crude product as a viscous orange oil (2.01 g, 67% mass recovery). ^{1}H NMR spectroscopic analysis of the crude material showed product contained both α-diazoacetate and methyl 2-phenylacetate starting material by comparison of the crude ^{1}H NMR spectrum with literature values for methyl 2-phenylacetate (~71 : 29 mixture of **76** : starting material).*,[127] The crude product (2.01 g, ~71: 29 mixture of **76** : starting material) was reused as starting material and the reaction was repeated using the same molar quantities as Method A, while following a procedure described by Davies and co-workers (Method B).[76] The ester (2.01 g, 11.42 mmol estimated to contain ~29 mol% methyl 2-phenylacetate starting material) and *p*-ABSA **77** (3.02 g, 12.57 mmol) were dissolved in acetonitrile (20 mL) while stirring at 0 °C. An acetonitrile solution (40 mL) of DBU (2.6 mL, 17.14 mmol) was added dropwise at 0 °C and the reaction mixture was stirred overnight at room temperature. TLC and infrared analysis confirmed completion of the reaction. Removal of solvent under reduced pressure provided the crude *α-diazoacetate* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) afforded the pure *α-diazoacetate* **76** [1.88 g, 93% mass recovery based on mixture obtained using Ford's conditions (Method A) and 53% overall yield based on starting material methyl 2-phenylacetate used for Method A] as a viscous orange oil; ν_{max}/cm^{-1} (film) 2954, 2090, 1706 br, 1599, 1576, 1500, 1450,

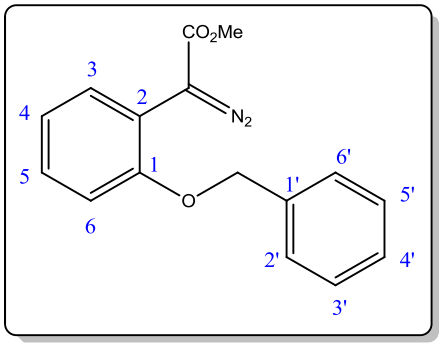
1436, 1354, 1334, 1288, 1250, 1194, 1155, 1052, 1026, 756, 691; δ_H (400 MHz, $CDCl_3$) 3.87 [3H, s, $OC\underline{H}_3$], 7.19 [1H, t with further unresolved splitting, *J* 7.2, aromatic <u>H</u>], 7.39 [2H, t with further unresolved splitting, *J* 7.6, 2 × aromatic <u>H</u>], 7.49 [2H, d with further unresolved splitting, *J* 7.6, 2 × aromatic <u>H</u>]. Spectral properties were consistent with previously reported data.[128]

* Characteristic signals for methyl 2-phenylacetate starting material in the crude ^{1}H NMR spectrum include two singlets at δ_H 3.63 ppm [0.3H] and δ_H 3.69 ppm [0.4H]. A characteristic stretch was observed in the infrared spectrum of the crude product; ν_{CO} 1741 cm^{-1}.

Method B: Davies' reported conditions[76]

Slightly modified molar ratios to those described by Davies[76] were employed here. Methyl 2-phenylacetate (3.50 g, 23.31 mmol) and *p*-ABSA **77** (6.16 g, 25.64 mmol) were dissolved in acetonitrile (40 mL) while stirring at 0 °C. An acetonitrile solution (40 mL) of DBU (5.2 mL, 30.0 mmol) was added dropwise at 0°C and the reaction mixture was stirred overnight at room temperature. TLC analysis and infrared spectroscopy confirmed completion of the reaction after stirring overnight at room temperature. Silica gel (*ca.* 25 g) was added to the reaction mixture and solvent was concentrated under reduced pressure. The solid residue was extracted with mixture of ethyl acetate and hexanes (10:90) and concentrated *in vacuo* to provide the crude *α-diazoacetate* as a viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) afforded the pure *α-diazoacetate* **76** (2.72 g, 66%) as a viscous orange oil. Spectral properties were consistent with previously reported data,[128] as well as data described above using Method A.

Methyl 2-[2-(benzyloxy)phenyl]-2-diazoacetate 116[110]

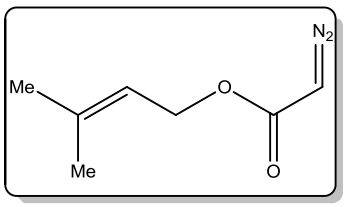


This was prepared following the procedure described for **76** using Ford's optimised conditions (Method A),[48] from methyl 2-[2-(benzyloxy)phenyl]acetate **129** (2.98 g, 11.64 mmol) and DBU (2.6 mL, 17.45 mmol) dissolved in distilled acetonitrile (30 mL) and the solution was stirred at 40 °C. A solution of *p*-ABSA **77** (3.08 g, 12.80 mmol and additional 3 × 0.1 equiv., 1.75 mmol) in distilled acetonitrile (50 mL) was added dropwise and the reaction mixture was stirred at 40 °C. The reaction progress was monitored by TLC analysis and after stirring for 2 h, the reaction appeared to be complete. Evaporation of solvent furnished the crude *α-diazoacetate* as a viscous orange oil (1.91 g, 64% mass recovery). Analysis of the crude material by ^{1}H NMR spectroscopy showed the product contained both α-diazoacetate and starting material by comparison with spectral data obtained for **129** above (~41 : 59 mixture of **116** : **129**).* The crude product (1.91 g, ~41 : 59 mixture of **116** : **129**) was reused as a starting material and the reaction was repeated using slightly modified conditions to those outlined by Hashimoto (Method B) using 2.0 equiv. *cf.* 3.0 equiv. *p*-ABSA **77**.[110] The phenylacetate ester **129** (1.91 g, ~41 : 59 mixture of **116** : **129**) and *p*-ABSA **77** (3.59 g, 14.94 mmol) were dissolved in distilled acetonitrile (40 mL) while stirring at 0 °C. An acetonitrile solution (40 mL) of DBU (4.5 ml, 29.88 mmol) was added dropwise at 0 °C and the reaction mixture was stirred overnight at room temperature. Silica gel (*ca.* 8 g) was added to the reaction mixture and solvent was concentrated under reduced pressure. The solid residue was extracted with mixture of ethyl acetate and hexanes (10:90) and concentrated *in vacuo* to

provide the crude *α-diazoacetate* as a viscous orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) afforded the pure *α-diazoacetate* **116** (1.55 g, 81% mass recovery based on mixture obtained from Method A and 47% overall yield based on starting material **129** used for Method A) as a viscous orange oil; ν_{max}/cm^{-1} (film) 2950, 2098, 1702, 1499, 1450, 1435, 1348, 1301, 1254, 1192, 1154, 1124, 1054, 1034, 750; δ_H (300 MHz, DMSO-d_6) 3.74 [3H, s, $CO_2C\underline{H}_3$], 5.16 [2H, s, $OC\underline{H}_2C_6H_5$], 7.04 [1H, ddd, *J* 13.8, 7.5, 1.2, aromatic <u>H</u>], 7.18 [1H, dd, *J* 8.4, 0.9, aromatic <u>H</u>], 7.27–7.52 [7H, m, 7 × aromatic <u>H</u>]; δ_C (75.5 MHz, DMSO-d_6)** 51.9 [CH_3, $CO_2\underline{C}H_3$], 58.6 [C, <u>C</u>=N_2], 69.9 [CH_2, $O\underline{C}H_2C_6H_5$], 112.6 [CH, <u>C</u>(6)H], 112.8 [C, <u>C</u>(2)]***, 121.0 [CH, <u>C</u>(4)H], 127.7 [2 × aromatic CH, <u>C</u>(3')H and <u>C</u>(5')H], 128.0 [CH, <u>C</u>(4')H], 128.4 [2 × aromatic CH, <u>C</u>(2')H and <u>C</u>(6')H], 128.9 [CH, <u>C</u>(3)H or <u>C</u>(5)H], 130.1 [CH, <u>C</u>(3)H or <u>C</u>(5)H], 136.3 [C, <u>C</u>(1')], 154.3 [C, <u>C</u>(1)$OCH_2C_6H_5$], 165.5 [C, <u>C</u>=O]. ^{1}H NMR and infrared spectral properties were consistent with previously reported data.[110]

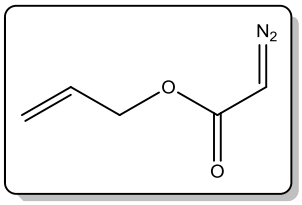
* Characteristic signals for starting material **129** in the crude ^{1}H NMR spectrum include three singlets at δ_H 3.63 ppm [0.3H], 3.69 ppm [0.4H] and 5.07 ppm [0.2H]. A characteristic stretch was also observed in the infrared spectrum of the crude material; ν_{CO} 1736 cm^{-1}.
** ^{1}H and ^{13}C NMR spectral data for **116** previously reported in the literature using C_6D_6 as solvent.[110]
*** Signal for quaternary carbon <u>C</u>(2) not identified in assignment by Hashimoto and co-workers.[110]

3-Methylbut-2-en-1-yl 2-diazoacetate 98[81,94]



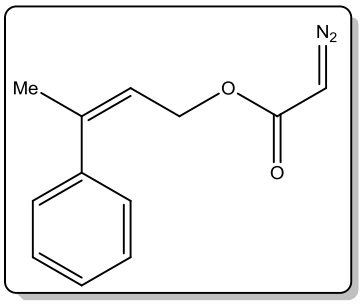
3-Methylbut-2-en-1-ol (1.2 mL, 11.61 mmol) and anhydrous sodium bicarbonate (2.93 g, 34.83 mmol) were placed in distilled acetonitrile (30 mL) and the reaction mixture was stirred at 0 °C. A solution of bromoacetyl bromide (1.5 mL, 17.42 mmol) in distilled acetonitrile (10 mL) was added dropwise to the reaction mixture. After stirring for 10 min, the reaction was quenched by addition of water (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried using magnesium sulfate and the solvent evaporated under reduced pressure to give the *α-bromoacetate* intermediate as a pale yellow oil which was used in the next step without purification. A solution of the *α-bromoacetate* intermediate in tetrahydrofuran (10 mL) was added to a solution of *N*,*N*′-ditosylhydrazine **96** (7.91 g, 23.22 mmol) in tetrahydrofuran (20 mL) and the reaction mixture was stirred at 0 °C. A tetrahydrofuran solution (10 mL) of DBU (8.7 mL, 58.05 mmol) was added dropwise to the reaction mixture over 10 min and the reaction mixture was stirred at 0 °C for 10 min. The reaction was subsequently quenched by addition of aqueous saturated sodium bicarbonate (15 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over magnesium sulfate and concentrated under reduced pressure to furnish the crude *α-diazocaetate* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) afforded the pure *α-diazoacetate* **98** (0.85 g, 47%) as a viscous orange oil; ν_{max}/cm^{-1} (film) 3119, 2975, 2937, 2918, 2111, 1694 br, 1445, 1392, 1359, 1344, 1239, 1181, 1001, 741; δ_H (400 MHz, $CDCl_3$) 1.72 [3H, s, one of C($C\underline{H}_3$)], 1.76 [3H, s, one of C($C\underline{H}_3$)], 4.66 [2H, d, *J* 7.2, $OC\underline{H}_2CH$], 4.75 [1H, br s, $C\underline{H}N_2$], 5.35 [1H, t with unresolved splitting, *J* 7.2, $OCH_2C\underline{H}$]. Spectral properties were consistent with previously reported data.[81]

Allyl 2-diazoacetate 97[32,80,81,94]



This was prepared following the procedure described for **98**, using prop-2-en-1-ol (1.2 mL, 17.22 mmol), bromoacetyl bromide (2.2 mL, 25.83 mmol), anhydrous sodium bicarbonate (4.34 g, 51.65 mmol) dissolved in distilled acetonitrile (40 mL). This was followed by addition of a solution of the *α-bromoacetate* intermediate in tetrahydrofuran (10 mL) to a tetrahydrofuran solution (20 mL) of *N*,*N*′-ditosylhydrazine **96** (11.72 g, 34.44 mmol) and subsequent addition of a solution of DBU (12.9 mL, 86.10 mmol) in tetrahydrofuran (20 mL) to give the crude *α-diazoacetate* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) to (10:90) afforded the pure *α-diazoacetate* **97** (0.64 g, 30%) as a bright yellow oil; ν_{max}/cm^{-1} (film) 3123, 3098, 2114, 1694 br, 1649, 1385, 1342, 1240, 1184, 1027, 993, 741; δ_H (400 MHz, $CDCl_3$) 4.66 [2H, dt, *J* 5.6, 1.2, $OC\underline{H}_2CHCH_2$], 4.78 [1H, br s, $C\underline{H}N_2$], 5.24 [1H, dd, *J* 10.8, 1.6, one of $OCH_2CHC\underline{H}_2$], 5.32 [1H, dd, *J* 17.2, 1.6, one of $OCH_2CHC\underline{H}_2$], 5.86–6.00 [1H, m, $OCH_2C\underline{H}CH_2$]. Spectral properties were consistent with previously reported data.[81]

(*E*)-3-Phenylbut-2-en-1-yl 2-diazoacetate 99[86,94]

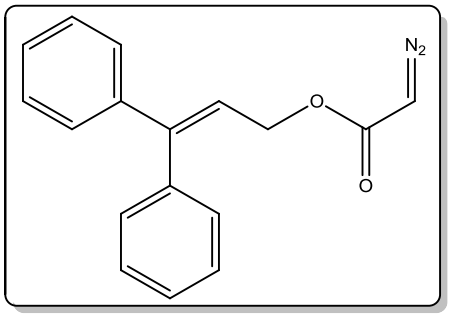


This was prepared following the procedure described for **98**, from (*E*)-3-phenylbut-2-en-1-ol **92** (1.10 g, 7.42 mmol), bromoacetyl bromide (1.0 mL, 11.13 mmol), anhydrous sodium bicarbonate (1.87 g, 22.27 mmol) dissolved in distilled acetonitrile (40 mL). This was followed by addition of a solution of the *α-bromoacetate* intermediate in tetrahydrofuran (10 mL) to a tetrahydrofuran solution (10 mL) of *N*,*N*′-ditosylhydrazine **96** (5.05 g, 14.84 mmol) and subsequent addition of a solution of DBU (5.6 mL, 37.11 mmol) in tetrahydrofuran (20 mL) to give the crude *α-diazoacetate* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) afforded the pure *α-diazoacetate* **99** (0.67 g, 42%)* as a bright yellow oil; ν_{max}/cm^{-1} (film) 3109, 2919, 2112, 1692, 1445, 1390, 1357, 1241, 1179; δ_H (400 MHz, $CDCl_3$) 2.13 [3H, s, $C\underline{H}_3$], 4.77 [1H, br s, $C\underline{H}N_2$], 4.89 [2H, d, *J* 6.8, $OC\underline{H}_2CH$], 5.90 [1H, t with additional unresolved coupling, *J* 6.8, $OCH_2C\underline{H}$], 7.20–7.44 [5H, m, 5 × aromatic $\underline{H}$]**. Spectral properties were consistent with previously reported data.[86]

* Reaction repeated using slightly modified conditions involving CH_3CN instead of THF and 1.2 equiv. DBU *cf.* 5.0 equiv. under the standard conditions. The α-diazoacetate **99** was isolated in 22% yield and spectral properties were consistent with those obtained above and in the literature.[86]

** Integration is higher than expected due to overlap with $CDCl_3$.

3,3-Diphenylallyl 2-diazoacetate 100[86,94]



This was prepared following the procedure described for **98**, using 3,3-diphenylprop-2-en-1-ol **93** (2.03 g, 9.40 mmol), bromoacetyl bromide (1.0 mL, 11.13 mmol), anhydrous sodium bicarbonate (1.26 g, 14.46 mmol) dissolved in distilled acetonitrile (40 mL). This was followed by addition of the a solution of the *α-bromacetate* intermediate in tetrahydrofuran (10 mL) to a tetrahydrofuran solution (20 mL) of *N*,*N*′-ditosylhydrazine **96** (6.62 g, 19.28 mmol) and subsequent addition of a solution of DBU (7.2 mL, 48.20 mmol) in tetrahydrofuran (20 mL) to furnish the crude *α-diazoacetate* as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) afforded the pure α-*diazoacetate* **100** (0.86 g, 32%) as a bright yellow oil; ν_{max}/cm^{-1} (film) 3112, 2111, 1694, 1495, 1445, 1389, 1362, 1240, 1177, 700; δ_H (400 MHz, $CDCl_3$) 4.73 [2H, d, *J* 7.2, $OC\underline{H}_2CH$], 4.76 [1H, br s, $C\underline{H}N_2$], 6.18 [1H, t, *J* 7.2, $OCH_2C\underline{H}$], 7.10–7.42 [10H, m, 10 × aromatic H]*. Spectral properties were consistent with previously reported data.[86]

Transition metal-catalysed transformations of α-diazoacetates

General procedure for Schlenk conditions in rhodium(II)-mediated reactions

A Schlenk tube or a three necked round-bottom flask fitted with a pressure equalising addition funnel and condenser (in case of reactions heated under reflux) was used in the reaction. All glassware was first flame dried under nitrogen. The set-up was attached to the vacuum/inert gas manifold *via* flexible tubing. Doubly distilled dichloromethane was added to the flask or Schlenk tube. The Schlenk stopcock was opened. The vacuum/inert manifold was opened to the vacuum for 20 seconds. The vacuum/inert gas manifold was then opened to the nitrogen and the round-bottom flask filled with nitrogen. This was repeated three times. The rhodium(II) catalyst was added at this point to the solvent and the system was again evacuated and refilled with nitrogen and stirred for 30 min at rt/–60 °C or heated under reflux for 3 h. A solution of α-diazoacetate in doubly distilled dichloromethane was added dropwise over ~30 min to a stirring solution at rt/–60 °C/reflux. The reaction mixture was stirred at rt/–60 °C/heated under reflux until infrared analysis confirmed consumption of starting material and completion of reaction.

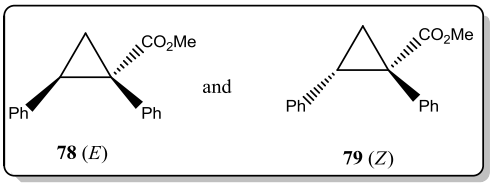
The purpose of carrying out reactions under these stringent conditions is to prevent the unwanted side reaction of molecular oxygen with metallocarbenoid to generate the 2,3-diketone by saturating the atmosphere with nitrogen. Flame drying all glassware prior to reaction helps eliminate adventitious water from reacting with metallocarbenoid to generate the α-hydroxyketone.

(i) Intermolecular cyclopropanations

General procedure for rhodium(II)-catalysed intermolecular cyclopropanation

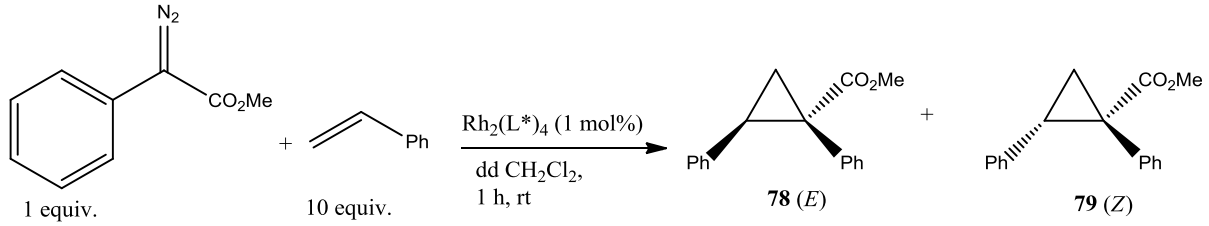
A solution of α-diazoacetate **76** (0.10 g, 1 equiv.) in doubly distilled dichloromethane (3 mL, further degassed using freeze, pump, thaw technique) was added dropwise over ~30 min to a stirring solution of rhodium(II) catalyst (1 mol%) and styrene (0.7 mL, 10 equiv.) in doubly distilled dichloromethane (5 mL) in a Schlenk tube. The reaction was carried out at room temperature under Schlenk conditions. The reaction mixture was stirred at this temperature until reaction completion was indicated by TLC and/or infrared analysis. The reaction mixture was concentrated under reduced pressure to give the crude product. Purification by column chromatography involved initial flushing of the column with hexane (to remove excess styrene) followed by using ethyl acetate/hexane (5:95) as eluent to afford the pure cyclopropane product.

(1*S*,2*R*)-Methyl 1,2-diphenylcyclopropanecarboxylate 78 (*E*) and (1*S*,2*S*)-Methyl 1,2-diphenylcyclopropanecarboxylate 79 (*Z*)[64,78]



A solution of methyl phenyldiazoacetate **76** (0.10 g, 0.57 mmol) in doubly distilled dichloromethane (3.0 mL) was added dropwise over 30 min to a stirring solution of $Rh_2(OAc)_4$ (2.8 mg, 1 mol%), styrene (0.7 ml, 5.68 mmol) in doubly distilled dichloromethane (5.0 mL) at room temperature under Schlenk conditions. The reaction mixture was stirred for 1 h at room temperature. The reaction progress was monitored by TLC and infrared spectroscopy and was complete after 1 h. The solvent was evaporated under reduced pressure to yield the crude *cyclopropane* as a green oil.^{1}H NMR analysis of the crude product allowed determination of the diastereomeric ratio by integration of the methoxy signals of the *E* and *Z* isomers (δ_H 3.32 ppm for *Z* and δ_H 3.66 ppm for *E*). Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (0:100) followed by (5:95) gave the pure *cyclopropane* **78** (*E*) as a colourless oil which solidified after storage at 5 °C overnight to afford a white solid (0.05 g, 37%); ν_{max}/cm^{-1} (film) 3029, 1718, 1499, 1433, 1259, 1211, 1162, 697; δ_H (400 MHz, $CDCl_3$) 1.88 [1H, dd, *J* 7.6, 4.8, one of C$\underline{H}_2$ of cyclopropane], 2.13 [1H, dd, *J* 9.2, 4.8, one of C$\underline{H}_2$ of cyclopropane], 3.11 [1H, dd, *J* 9.2, 7.6, PhC$\underline{H}$], 3.66 [3H, s, OC$\underline{H}_3$], 6.73–6.80 [2H, m, 2 × aromatic $\underline{H}$], 6.98–7.08 [5H, m, 5 × aromatic $\underline{H}$], 7.10–7.15 [3H, m, 3 × aromatic $\underline{H}$]. Spectral properties were consistent with previously reported data.[64,78]

Table 3.15 *Rhodium(II)-catalysed intermolecular cyclopropanations of* **78** (*E*)[a]



1 equiv. **76** | 10 equiv. | **78** (*E*) | **79** (*Z*)

Entry	Catalyst	Time (h)	Solvent	**78** (*E*) **: 79** (*Z*)[b]	Yield **78** (*E*) **(%)**[c]	ee of **78** (*E*) **(%)**[d,e]
1	$Rh_2(OAc)_4$ **1**	1.0	DCM	98 : 2	69	–[78]
2	$Rh_2(OAc)_4$ **1**	1.0	DCM	99 : 1	37	~0[f]
3	Rh_2(*S*-BSP)$_4$ **6**	1.0	DCM	97 : 3	45	60 (1*R*,2*S*)[64]
4	Rh_2(*S*-DOSP)$_4$ **9**	1.0	DCM	98 : 2	69	69 (1*R*,2S)[78]
5	Rh_2(*S*-DOSP)$_4$ **9**	1.0	DCM	–	40	69 (1*R*,2*S*)
6	Rh_2(*S*-PTTL)$_4$ **13**	1.0	DCM	98 : 2	95	34 (1*S*,2*R*)[64]
7	Rh_2(*S*-PTTL)$_4$ **13**	1.0	DCM	–	43	21 (1*S*,2*R*)
8	Rh_2(*R*-*p*-MeOMand)$_4$ **51**	1.0	DCM	98 : 2	41	16 (1*R*,2*S*)
9	Rh_2(*R*-*p*-ClMand)$_4$ **50**	1.0	DCM	98 : 2	44	~0[f]
10	Rh_2(*R*-diFMand)$_4$ **52**	1.0	DCM	98 : 2	92	~0[f]
11	Rh_2(*S*-α-Phpa)$_4$ **53**	1.0	DCM	>99 : 1	59	18 (1*S*,2*R*)
12	Rh_2('A'-MPA)$_4$ **54/55**	1.0	DCM	99 : 1	49	18 (1*S*,2*R*)
13	Rh_2('B'-MPA)$_4$ **54/55**	1.0	DCM	99 : 1	76	9 (1*S*,2*R*)
14	Rh_2('A'-MNA)$_4$ **56/57**	1.0	DCM	98 : 2	65	8 (1*R*,2*S*)
15	Rh_2('B'-MNA)$_4$ **56/57**	1.0	DCM	98 : 2	71	~0[f]
16	Rh_2('B'-MBrPA)$_4$ **58/59**	1.0	DCM	97 : 3	43	15 (1*S*,2*R*)
17	Rh_2('A'-BBrPA)$_4$ **60/61**	1.0	DCM	99 : 1	53	18 (1*R*,2*S*)

[a] Reactions conducted using the general procedure for rhodium(II)-catalysed intermolecular cyclopropanation.
[b] Ratios based on integration of the methyl ester ($CO_2C\underline{H}_3$) signals from the ^{1}H NMR spectra of the crude products.
[c] Yield of **78** (*E*) following column chromatography.
[d] Determined by chiral stationary phase HPLC on material **78** (*E*) after chromatography (see *Appendix IV* for details).
[e] Entries 1, 3, 4, 6 refer to literature data.[64,78] Assignment of stereochemistry of the products is by comparison with previously reported data.[64,78]
[f] When the enantiomeric excess was ≤ 5% the sample was regarded as achiral.

(ii) Intramolecular cyclopropanations

General procedure for rhodium(II)-catalysed intramolecular cyclopropanation

A solution of α-diazoacetate (0.10 g, 1 equiv.) in doubly distilled dichloromethane (3 mL, further degassed using freeze, pump, thaw technique) was added dropwise over ~30 min to a stirring solution of rhodium(II) catalyst (1 mol%) in doubly distilled dichloromethane (3 mL) in a three necked round-bottom flask. The reaction was carried out at room temperature/under reflux and using Schlenk conditions in some cases as indicated. The mixture was stirred at this temperature until reaction completion was indicated by TLC and/or infrared analysis. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product. Purification by column chromatography gave a mixture of products with the cyclopropane **103** found to co-elute with water insertion product **105**.

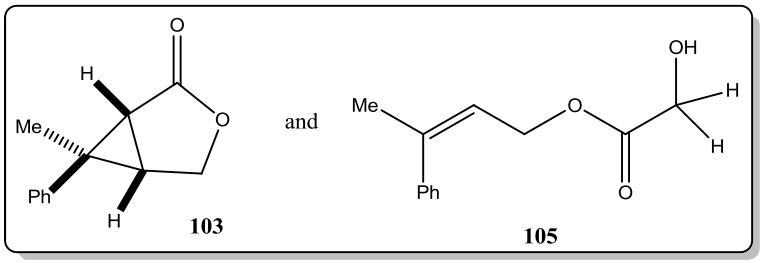
A modified procedure involved addition of a solution of α-diazoacetate (0.10 g, 1 equiv.) in doubly distilled dichloromethane (40 mL) dropwise over 1.5 h to a refluxing solution of

rhodium(II) catalyst (1 mol%) in doubly distilled dichloromethane (30 mL) in a three necked round-bottom flask. The reaction was conducted under Schlenk conditions in some cases. The reaction mixture was heated under reflux until the reaction was deemed complete by TLC and/or infrared analysis. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to provide the crude product(s). Purification by column chromatography gave a mixture of products with the cyclopropane **102** found to co-elute with water insertion product **110**. When purification was attempted using Kugelrohr distillation, the cyclopropane **102** could not be separated from Unknown B **113**.

Isolated products from intramolecular cyclopropanations of α-diazoacetate 99

6-Methyl-6-phenyl-3-oxabicyclo[3.1.0]hexan-2-one 103[86] and (*Z*)-3-phenylbut-2-en-1-yl 2-hydroxyacetate 105

Isolated from reaction in the presence of Rh_2(*S*-PTTL)$_4$ **13** at room temperature (**Table 3.15**, entry 1)

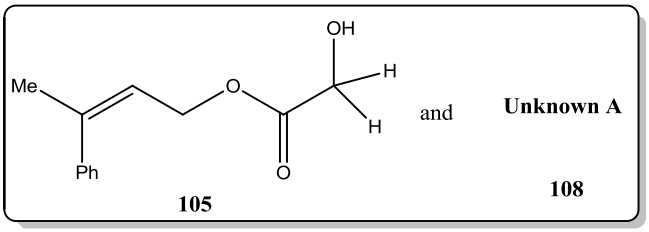


103 **105**

Colourless oil (0.04 g) contains both **103** and **105** in ~1 : 1 mixture of **103** : **105**; δ_H (400 MHz) (cyclopropane **103**) 1.49 [3H, s, C$\underline{H}_3$], 2.46 [1H, d with further unresolved splitting, *J* 6.4, one of C$\underline{H}$ of cyclopropane], 2.54 [1H, t with further unresolved splitting, *J* 6.8 one of C$\underline{H}$ of cyclopropane], 4.36 [1H, d with further unresolved splitting, *J* 10.0, one of OC$\underline{H}_2$], 4.54 [1H, dd, *J* 10.0, 5.6, one of OC$\underline{H}_2$], 7.25–7.40 [5H, m, 5 × aromatic $\underline{H}$]. Spectral properties for cyclopropane **103** were consistent with previously reported data.[86] Signals for the co-eluting α-hydroxyketone **105** were consistent with those from isolated sample below (**Table 3.15**, entry 3).

(*Z*)-3-Phenylbut-2-en-1-yl 2-hydroxyacetate 105 and Unknown A 108

Isolated from reaction in the presence of Rh_2(oct)$_4$ **4** at room temperature (**Table 3.15**, entry 3)



105 **108**

Colourless oil **105** (0.03 g, 31%) (less polar fraction); δ_H (400 MHz) 2.14 [3H, s, C$\underline{H}_3$], 2.44 [1H, br s, CH$_2$O$\underline{H}$], 4.20 [2H, s, COC$\underline{H}_2$OH], 4.92 [2H, d, *J* 7.2, OC$\underline{H}_2$CH], 5.89 [1H, tq, *J*

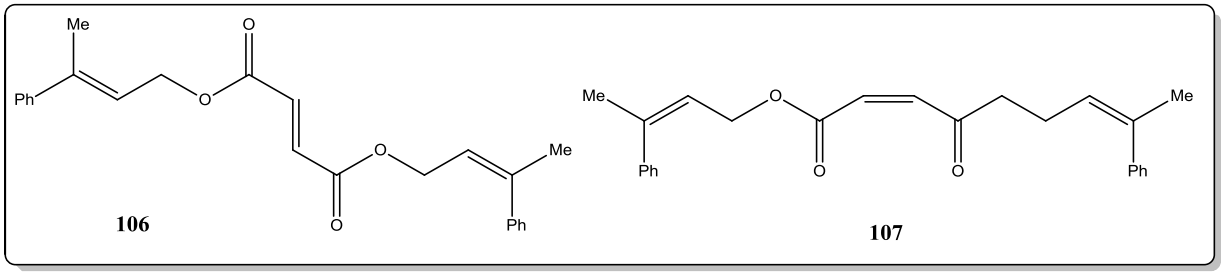
7.2, 1.2, $OCH_2C\underline{H}$], 7.24–7.44 [5H, m, 5 × aromatic $\underline{H}$]; HRMS (ES+): Exact mass calculated for $C_{12}H_{15}O_3$ $[M+H]^+$, 207.1021. Found 207.1228. m/z (ES+) 207.5 $[(M+H)^+$, 22%].* ^1H NMR properties for **105** were in agreement with signals observed in other reactions [**Table 3.15**, entries 1 and 2 (0.05 g, 48%)].

* HRMS was obtained on sample from $Rh_2(OAc)_4$-catalysed reaction (**Table 3.15**, entry 2).

Unknown A **108** (colourless oil, 0.01 g) (more polar fraction), δ_H (400 MHz) 2.13 [3H, s], 3.16 [1H, d, *J* 7.6], 4.61 [1H, d, *J* 7.2], 4.89–5.04 [2H, m], 5.91 [1H, ddd, *J* 8.4, 7.2, 1.2], 7.27–7.43 [5H, m].

(*E*)-3-Phenylbut-2-en-1-yl [(*Z*)-3-phenylbut-2-en-1-yl] fumarate* 106 and (2*Z*,7*Z*)-(*Z*)-3-phenylbut-2-en-1-yl 4-oxo-8-phenylnona-2,7-dienoate 107

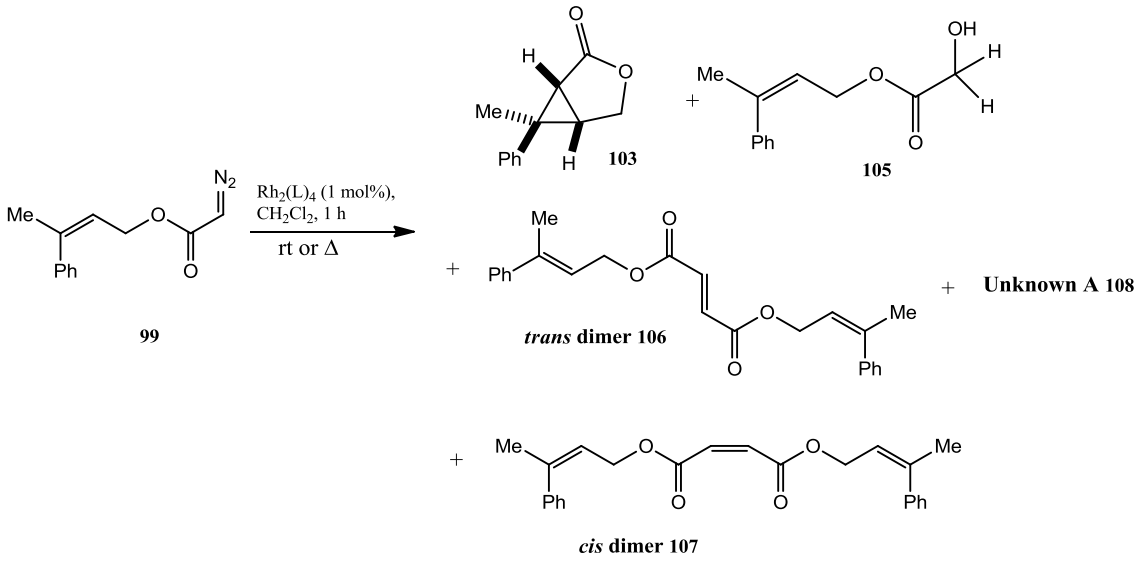
Isolated from reaction in the presence of $Rh_2(OAc)_4$ **1** under Schlenk conditions (**Table 3.15**, entry 2)



Colourless oil **106** (0.01 g, 5%); δ_H (400 MHz) 2.14 [6H, s, $CHC\underline{H}_3$], 4.92 [4H, d, *J* 7.2, $OC\underline{H}_2CH$], 5.92 [2H, tq, *J* 7.2, 1.6, $OCH_2C\underline{H}$], 6.91 [2H, s, $COC\underline{H}$], 7.22–7.43 [10H, m, 10 × aromatic $\underline{H}$]. The crude product appeared to contain both *trans* and *cis* dimers, **106** and **107** in ~1.0 : 1.22 mixture of **106** : **107** by ^1H NMR analysis. The singlets at δ_H 6.30 ppm and 6.91 ppm were ascribed to the *cis* and *trans* isomers respectively, with only the *trans* isomer **106** isolated after chromatographic purification.

* Assigned as *trans* isomer by comparison with signals for diethyl fumarate and diethyl maleate in the literature (δ_H 6.85 *vs.* 6.24 ppm for *trans* and *cis* respectively).[98]

Table 3.16 *Rhodium(II)-catalysed intramolecular cyclopropanations of* **99**[a]



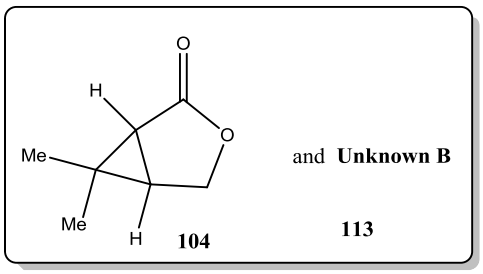
Entry	Catalyst	Temp.	Yield (%)[b]	Crude ratio 103 : 105 : 106 : 107 : 108	Purified ratio 103 : 105
1	Rh_2(*S*-PTTL)$_4$ **13**	rt	42	n/a[c] : n/a[c] : – : – : –	1.0[d] : 0.89[d]
2	$Rh_2(OAc)_4$ **1**	rt	63	– : 19.0[e] : 1.0[e] : 1.22[e,f] : –	– : –
3	$Rh_2(oct)_4$ **4**	rt	54	Trace[e] : 14.1[e] : 1.0[e] : 1.17[e,f] : 3.21[e]	– : –
4	Rh_2(*S*-PTTL)$_4$ **13**	reflux	52	n/a[c] : n/a[c] : – : – : –	1.0[d] : 2.19[d]

[a] Reaction conducted using the general procedure for rhodium(II)-catalysed intramolecular cyclopropanation reactions.
[b] Combined yield of all isolated products from the reaction mixture.
[c] In this reaction, n/a refers that the crude ratios were not determined.
[d] Cyclopropane **103** not isolated cleanly and co-eluted with O–H insertion product **105**. The ratio is assigned from integration of the purified mixture and not from ^{1}H NMR of the crude material.
[e] Ratio assigned by integration of the crude reaction mixture.
[f] Signal at δ_H 6.30 ppm in the crude mixture assumed to be the *cis* dimer **107**.

Isolated products from intramolecular cyclopropanations of α-diazoacetate 98

6,6-Dimethyl-3-oxabicyclo[3.1.0]hexan-2-one 104[81] and Unknown B 113

Isolated from reaction in the presence of Rh_2(*S*-PTTL)$_4$ at reflux with product purified by Kugelrohr distillation (**Table 3.16**, entry 4)



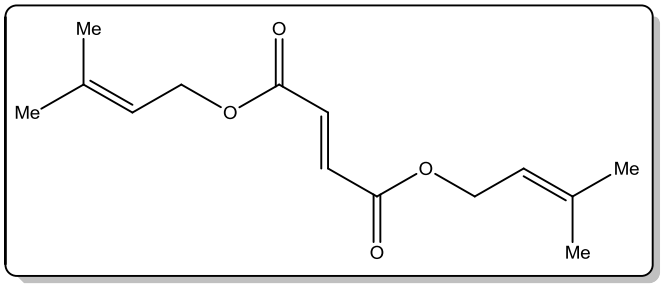
Colourless oil contains both **104** and **113** in a 1.03 : 1.0 mixture of **104** : **113*** (0.06 g); b.p. 130 °C at 15 mmHg (lit.,[81] 120 °C at 15 mmHg); ν_{max}/cm^{-1} (film) 2917, 1770, 1748, 1450, 1381, 1362, 1179, 1094, 1049; δ_H (400 MHz)** 1.17 [3H, s, one of CC<u>H</u>$_3$], 1.18 [3H, s, one

of CC$\underline{H}_3$], 1.95 [1H, dd, *J* 6.0, 0.8, one of C$\underline{H}$ of cyclopropane], 2.05 [1H, t with further unresolved splitting, *J* 6.4, one of C$\underline{H}$ of cyclopropane], 4.15 [1H, d, *J* 9.6, one of OC$\underline{H}_2$], 4.37 [1H, dd, *J* 10.0, 5.6, one of OC$\underline{H}_2$]; m/z (ES+) 127.3 [$(M+H)^+$, 40%]. Spectral properties for cyclopropane **104** were consistent with previously reported data.[81] Spectral data for Unknown B **113**; δ_H (400 MHz) 1.72 [1.7H, s], 1.73 [1.4H, s,], 1.76 [2.3H, s], 1.77 [1.8H, s], 4.63–4.68 [2H, symmetrical m], 5.32–5.39 [1H, m].

* Cyclopropane **104** was not isolated cleanly and was found to co-distill with an unknown product **113** following Kugelrohr distillation. The ratio of the mixture is assigned by integration of the ^{1}H NMR spectrum of the purified sample and not from ^{1}H NMR of the crude material.
** *Cis* and *trans* dimers also present in purified sample ~15 mol% and observed as a 2.4 : 1 mixture of *cis* **112** : *trans* **111**.

bis(3-Methylbut-2-en-1-yl) fumarate* 111

Isolated from reaction in the presence of $Rh_2(oct)_4$ at reflux with addition of **98** over 1.5 h (**Table 3.16**, entry 3)

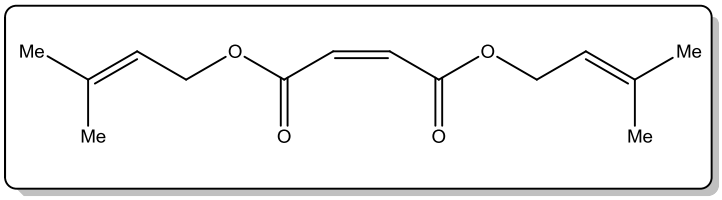


Colourless oil (0.02 g, 11%) (less polar fraction); δ_H (400 MHz) 1.73 [6H, s, one of CC$\underline{H}_3$], 1.77 [6H, s, one of CC$\underline{H}_3$], 4.69 [4H, d, *J* 7.2, OC$\underline{H}_2$CH], 5.37 [2H, t with further unresolved splitting, *J* 7.2, OCH$_2$C$\underline{H}$], 6.85 [2H, s, COC$\underline{H}$]; m/z (ES+) 253.4 [$(M+H)^+$, 44%].

* Assigned as *trans* isomer by comparison with signals for diethyl fumarate and diethyl maleate in the literature (δ_H 6.85 *vs.* 6.24 ppm for *trans* and *cis* respectively).[98]

bis(3-Methylbut-2-en-1-yl) maleate* 112

Isolated from reaction in the presence of $Rh_2(oct)_4$ at reflux with addition of **98** over 1.5 h (**Table 3.16**, entry 3)

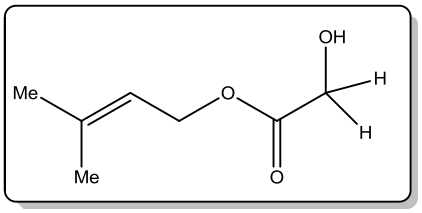


Colourless oil (0.01 g, 6%) (more polar fraction); δ_H (400 MHz) 1.72 [6H, s, one of CC$\underline{H}_3$], 1.77 [6H, s, one of CC$\underline{H}_3$], 4.69 [4H, d, *J* 7.2, OC$\underline{H}_2$CH], 5.37 [2H, t with further unresolved splitting, *J* 7.2, OCH$_2$C$\underline{H}$], 6.22 [2H, s, COC$\underline{H}$].

* Assigned as *cis* isomer by comparison with signals for diethyl fumarate and diethyl maleate in the literature (δ_H 6.85 *vs.* 6.24 ppm for *trans* and *cis* respectively).[98]

3-Methylbut-2-en-1-yl 2-hydroxyacetate 110

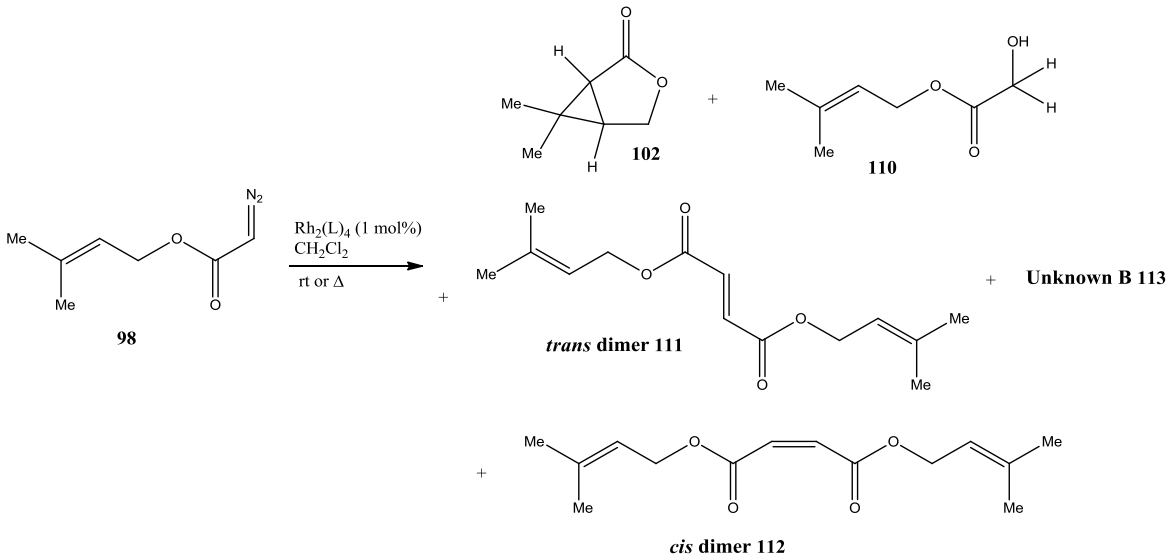
Detected in the crude product of reaction in the presence of $Rh_2(oct)_4$ at room temperature (**Table 3.16**, entry 2)



Colourless oil (0.08 g); δ_H (400 MHz)* 1.71 [2H, s, one of CC<u>H</u>$_3$], 1.76 [2H, s, one of CC<u>H</u>$_3$], 2.58 [1H, br s, CH$_2$O<u>H</u>], 4.14 [2H**, s, COC<u>H</u>$_2$OH]***, 4.69 [2H, d, *J* 7.2, OC<u>H</u>$_2$CH], 5.32–5.37 [1H, m, OCH$_2$C<u>H</u>].

* ^{1}H NMR signals are tentatively assigned as there is overlap between relevant signals of **110** and the minor dimeric components **111** and **112.**
** Integration of signal is lower than expected at ~1H.
*** Another signal at δ_H 4.21 ppm may be ascribed to C<u>H</u>$_2$OH.

Table 3.17 *Rhodium(II)-catalysed intramolecular cyclopropanation of* **98**[a]



Entry	Catalyst	Temp.	Yield (%)[b]	Crude ratio 102 : 110 : 111 : 112 : 113	Purified ratio 102 : 111 : 112 :113
1	Rh_2(*S*-DOSP)$_4$ **9**	rt	29	n/a[c] : n/a[c] : n/a[c] : – : –	3.46[d] : 1.0[d] : 1.61[d] : –
2	$Rh_2(oct)_4$ **4**	rt	34	– : 29.8[e] : 1.0[e] : 1.0[e] : –	– : – : – : –
3	$Rh_2(oct)_4$ **4**	reflux	53	1.0[e] : – : 1.01[e] : 1.05[e] : –	– : – : – : –
4	Rh_2(*S*-PTTL)$_4$ **13**	reflux	73	1.0[e] : – : 0.06[e] : 0.18[e] :1.51[e]	1.03[d] : – : – : 1.0[d]

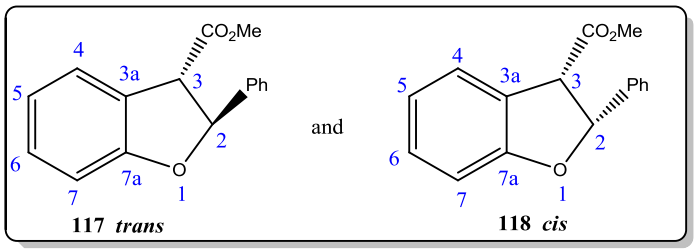
[a] Reactions conducted using the general procedure for rhodium(II)-catalysed intramolecular cyclopropanation.
[b] Combined yield of all isolated products from the reaction mixture.
[c] In this reaction, n/a refers that the crude ratios were not determined.
[d] Ratio is assigned from ^{1}H NMR integration of the purified product and not from integration of the crude material. Signal for C<u>H</u>$_2$OH appears to be present at δ_H 4.23 ppm.
[e] Ratio is based on ^{1}H NMR integration of the crude reaction mixture.

(iii) Intramolecular C–H insertion reactions

General procedure for rhodium-catalysed intramolecular C–H insertion reactions

A solution of α-diazoacetate **116** (0.10 g, 1 equiv.) in doubly distilled dichloromethane (3 mL, further degassed using freeze, pump, thaw technique) was added dropwise over ~30 min to a stirring solution of rhodium(II) catalyst (1 mol%) in doubly distilled dichloromethane (5 mL) in a Schlenk tube. The reaction was carried out at room temperature, –60 °C or –78 °C under Schlenk conditions. The mixture was stirred at this temperature until reaction completion was indicated by TLC and/or infrared analysis. For reactions under cryogenic conditions, the reaction mixture was warmed to room temperature and then concentrated under reduced pressure to provide the crude product(s). The diastereomeric ratio was determined from ^{1}H NMR analysis of the crude product(s) and tended to favour the *trans* dihydrobenzofuran **117** in most cases. Purification by column chromatography involved using ethyl acetate/hexane (5:95) as eluent to afford the purified dihydrobenzofurans **117** and **118**. Isolation of the two diastereomers was achieved in all examples using the catalysts developed by Ford,[48] as well as the commercial Rh_2(*S*-PTPA)$_4$ **14** catalyst, in accordance with the literature.[110] Reactions in the presence of Rh_2(*S*-PTTL)$_4$ **13** catalyst furnished the *cis* dihydrobenzofuran **118** only, which is consistent with literature reports.[110]

(2*S*,3*S*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 117 and (2*R*,3*R*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 118[110]



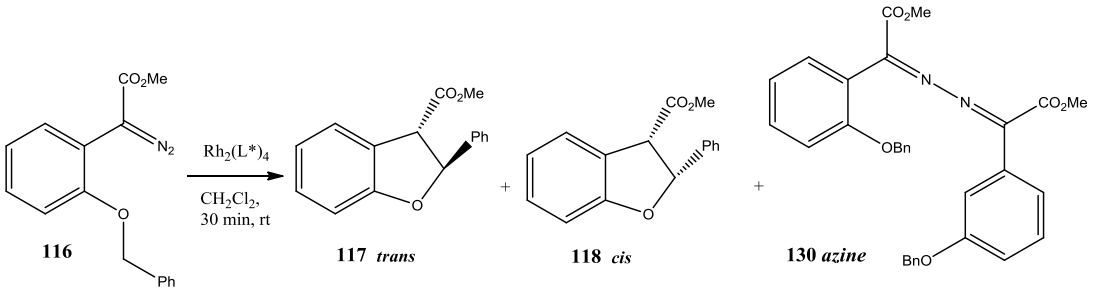
A solution of methyl 2-[2-(benzyloxy)phenyl]-2-diazoacetate **116** (0.10 g, 0.35 mmol) in doubly distilled dichloromethane (3 mL) was added dropwise over 30 min to a stirring solution of Rh_2(*S*-PTPA)$_4$ **14** (5.2 mg, 1 mol%) in doubly distilled dichloromethane (3 mL) under Schlenk conditions. The reaction mixture was stirred for 0.5 h at rt and the reaction progress was monitored by TLC analysis and infrared spectroscopy. Evaporation of the solvent under reduced pressure afforded the crude *dihydrobenzofurans* as a green oil. Purification was carried out by column chromatography on silica gel with ethyl acetate/hexane (5:95) as eluent to furnish the pure *dihydrobenzofurans*. The less polar compound, colourless needles (0.003 g, 4%) were assigned as **117** {(2*S*,3*S*), *trans*} and the more polar compound, a colourless oil (0.016 g, 17%) was assigned as **118** {(2*R*,3*S*) *cis*}. Visualisation was aided using phosphomolybdic acid stain. {(2*S*,3*S*), 8% ee} **117**; ν_{max}/cm^{-1} (film) 3300, 2923, 1740, 1596, 1475, 1237; δ_H (400 MHz, $CDCl_3$) 3.83 [3H, s, CO_2CH_3], 4.28 [1H, d, *J* 7.2, C(3)H], 6.11 [1H, d, *J* 7.2, C(2)H], 6.93 [2H, t, *J* 8.4, 2 × aromatic H], 7.20–7.44 [7H, m, 7 × aromatic H]*. Spectral properties were consistent with previously reported data.[110]

{(2*R*,3*S*), 63% ee} **118**; ν_{max}/cm^{-1} (film) 2951, 2111 (azine), 1736, 1598, 1480, 1456, 1431, 1237; δ_H (400 MHz, $CDCl_3$) 3.21 [3H, s, CO_2CH_3], 4.62 [1H, d, *J* 10.0, C(3)H], 5.99 [1H, d, *J* 10.0, C(2)H], 6.96 [2H, t, *J* 7.6, 2 × aromatic H], 7.18–7.41 [7H, m, 7 × aromatic H]**. Spectral properties were consistent with previously reported data.[110]

Polarimetry data was obtained from **Table 3.18**, entry 14, using toluene at −60 °C and Rh_2('A'-MPA)$_4$ **54**/**55** as catalyst and the reaction was conducted on a larger scale than usual (× 3.8 times scale of the standard reaction). (2*R*,3*R*) **117**; $[\alpha]_D^{20}$ −39.11 (*c* 1.12, $CHCl_3$) for 75% ee***, [lit.,[110] $[\alpha]_D^{21}$ −58.2 (*c* 1.12, $CHCl_3$) for 80% ee] and (2*R*,3*S*) **118**; $[\alpha]_D^{20}$ +29.4 (*c* 1.00, $CHCl_3$) for 67% ee, [lit.,[110] $[\alpha]_D^{21}$ +57.9 (*c* 1.00, $CHCl_3$) for 70% ee] were isolated, thereby confirming the absolute stereochemistry.

Note: Enantiopurities were slightly lower for compounds **117** and **118** obtained using scaled-up reaction compared to the standard screening conditions (**Table 3.18**, entry 13 *vs.* 14).
* Integration is higher than expected due to overlap with $CDCl_3$.
** Integration is higher than expected due to overlap of $CDCl_3$ and azine side product.
*** See footnote *j* in **Table 3.18**.

Table 3.18 *Rhodium(II)-catalysed intramolecular C–H insertion reactions of* **116**[a]



Entry	Catalyst	Solvent	Temp. (°C)	*Trans*-117: *cis* 118[b]	Yield (%)[c] 117	Yield (%)[c] 118+130	Ratio 118 : 130[d]	ee (%)[e,f] 117 *trans*	118 *cis*
1	$Rh_2(OAc)_4$ **1**	DCM	rt	73 : 27	10	8	1.0 : 2.26	~0[g]	
2	Rh_2(*S*-PTTL)$_4$ **13**	DCM	–45	1 : >99	–	63	–		90 (2*R*,3*S*)[110]
3	Rh_2(*S*-PTTL)$_4$ **13**	DCM	rt	1 : >99	–	26	16.0 : 1.0		92 (2*R*,3*S*)
4	Rh_2(*S*-PTTL)$_4$ **13**	DCM	–60	2 : 98	–	64	23.5 : 1.0		93 (2*R*,3*S*)
5	Rh_2(*S*-PTPA)$_4$ **14**	Toluene	–60	30 : 70	27	59	–	80 (2*R*,3*R*)	70 (2*R*,3*S*)[110]
6	Rh_2(*S*-PTPA)$_4$ **14**	DCM	rt	25 : 75	4	17	13.3 : 1.0	8 (2*S*,3*S*)	63 (2*R*,3*S*)
7	Rh_2(*R*-*p*-ClMand)$_4$ **50**	DCM	rt	68 : 32	12	7	1.97 : 1.0	65 (2*S*,3*S*)	16 (2*R*,3*S*)
8	Rh_2(*R*-*p*-MeOMand)$_4$ **51**	DCM	rt	57 : 43	30	48	4.12 : 1.0	60 (2*S*,3*S*)	23 (2*R*,3*S*)
9	Rh_2(*R*-p-MeOMand)$_4$ **51**	Toluene	rt	43 : 57	31	40	13.3 : 1.0	54 (2*S*,3*S*)[h]	6 (2*S*,3*R*)
10	Rh_2(*R*-diFMand)$_4$ **52**	DCM	rt	64 : 36	13	14	4.12 : 1.0	~0[g]	
11	Rh_2(*S*-α-Phpa)$_4$ **53**	DCM	rt	56 : 44	29	25	6.25 : 1.0	6 (2*R*,3*R*)	10 (2*S*,3*R*)
12	Rh_2('A'-MPA)$_4$ **54/55**	DCM	rt	57 : 43	19	17	7.27 : 1.0	83 (2*R*,3*R*)	54 (2*S*,3*R*)
13	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–60	82 : 18	64[i]	64[i]	–	86 (2*R*,3*R*)[j]	83 (2*S*,3*R*)[k]
14[l]	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–60	90 : 10	22	12	1.0 : 1.35	75 (2*R*,3*R*)[j]	67 (2*S*,3*R*)
15	Rh_2('A'-MPA)$_4$ **54/55**	Toluene	–78	91 : 9	96[i]	96[i]	1.0 : 2.65	86 (2*R*,3*R*)	71 (2*S*,3*R*)[k]
16	Rh_2('B'-MPA)$_4$ **54/55**	DCM	rt	33 : 67	26	25	4.26 : 1.0	77 (2*S*,3*S*)	42 (2*R*,3*S*)
17	Rh_2('B'-MPA)$_4$ **54/55**	Hexane	rt	23 : 77	12	27	3.39 : 1.0	69 (2*S*,3*S*)	48 (2*R*,3*S*)
18	Rh_2('A'-MNA)$_4$ **56/57**	DCM	rt	58 : 42	10	15	2.05 : 1.0	62 (2*R*,3*R*)[j]	27 (2*S*,3*R*)
19	Rh_2('A'-MNA)$_4$ **56/57**	Toluene	rt	80 : 20	41	36	3.96 : 1.0	58 (2*R*,3*R*)[h]	45 (2*S*,3*R*)
20	Rh_2('B'-MNA)$_4$ **56/57**	DCM	rt	56 : 44	9	23	3.15 : 1.0	11 (2*R*,3*R*)[j]	~0[g]
21	Rh_2('B'-MNA)$_4$ **56/57**	DCM	rt	56 : 44	9	23	3.15 : 1.0	44 (2*R*,3*R*)[k]	~0[g]
22	Rh_2('B'-MBrPA)$_4$ **58/59**	DCM	rt	50 : 50	6	14	1.69 : 1.0	70 (2*S*,3*S*)[j]	50 (2*R*,3*S*)
23	Rh_2('A'-BBrPA)$_4$ **60/61**	DCM	rt	36 : 64	3	7	4.70 : 1.0	72 (2*S*,3*S*)[j]	42 (2*R*,3*S*)
24	Rh_2('A'-BBrPA)$_4$ **60/61**	Toluene	rt	66 : 34	42	29	7.40 : 1.0	68 (2*R*,3*R*)[h]	42 (2*S*,3*R*)[k]

[a] Reactions conducted using the general procedure for rhodium-mediated intramolecular C–H insertion reactions.

[b] Ratios based on integration of the methyl ester ($CO_2C\underline{H}_3$) signals from the ^{1}H NMR spectra of the crude products.

[c] Combined yield of **117, 118** and **130** following column chromatography. While **117** can be separated, **118** and **130** are isolated as a combined fraction.

[d] Ratios based on integration of assumed benzylic signals for *cis* and *trans* azine **130** at δ_H ~5.09 ppm and signal for **118** at δ_H 5.99 ppm (Ar$\underline{H}$) in the ^{1}H NMR spectrum of the purified mixed fraction of **118** and **130.**

[e] Determined by chiral stationary phase HPLC on material **117** and **118** obtained after chromatography (see *Appendix IV* for details).

[f] Entries 2 and 5 refer to literature data.[110] Assignment of stereochemistry of the products is by comparison with previously reported data.[110]

[g] Where enantiomeric excess was ≤ 5% the sample was regarded as achiral.

[h] In retrospect, samples used for chiral HPLC analysis were too concentrated and as a result the % ee is likely to be underestimated.

[i] Samples of **117** and **118/130** not isolated and corresponds to the overall yield of purified mixed fraction **117/118/130**.

[j] Enantiopurity is based on integration of peaks for **117** using Chiralcel OD-H column. Earlier work has helped distinguish between the enantiomers for **117**; t_R 5.1 min (2*R*,3*R*) and t_R 6.2 min (2*S*,3*S*).

[k] Signals on the HPLC not fully resolved and therefore, enantiopurities are estimated rather than exact.

[l] Reaction carried out on a larger scale than usual (× 3.8 times usual scale) to provide samples for optical rotation analysis.

3.6 Reference List

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Appendices

Your success story is a bigger story than whatever you're trying to say on stage... Success makes life easier. It doesn't make living easier.

Bruce Springsteen

To live as gently as I can;
To be, no matter where, a man;
To take what comes of good or ill
And cling to faith and honour still;
To do my best, and let that stand
The record of my brain and hand;
And then, should failure come to me,
Still work and hope for victory.

To have no secret place wherein
I stoop unseen to shame or sin;
To be the same when I'm alone
As when my every deed is known;
To live undaunted, unafraid
Of any step that I have made;
To be without pretence or sham
Exactly what men think I am.

Edgar Albert Guest, "My Creed".

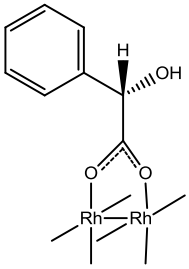
Appendix I List of abbreviations

ABq	AB quartet
Ac	acyl
aq.	aqueous
Ar	aryl
atm	atmospheres
BBrPA	(1*S*,2*R*)-bornyloxy-4-bromo-phenylacetic acid
bmim	1-butyl-3-methylimidazolium
Bn	benzyl
Boc	di-*tert*-butyl dicarbonate
b.p.	boling point
BPI	bis(pyridineimine)isoindoles
br	broad
br d	broad doublet
br s	broad singlet
Bu	butyl
Bt	benzotriazole
BtMs	mesylated benzotriazole
BTMSM	bis(trimethylsilyl)methyl
c	concentration
ca.	circa
cat.	catalytic amount
Cbz	carboxybenzyl
cf.	compare or confer
C–H	carbon–hydrogen
CHT	cycloheptatriene
cm	centimetre
conc.	concentrated
COSY	correlation spectroscopy
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
de	diastereomeric excess
DEPT	distortionless enhancement of polarisation transfer
DIBAl-H	diisobutylaluminium hydride
DIC	diisopropylcarbodiimide
DMAD	dimethylacetylene dicarboxylate
DMAP	4-(dimethylamino)pyridine
DMB	2,2-dimethylbutane
DMD	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dr	diastereomeric ratio

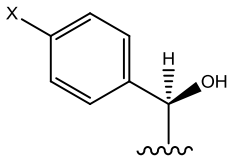
dt	doublet of triplets
EAG	electron-withdrawing group
EDA	ethyl diazoacetate
EDG	electron-donating group
ee	enantiomeric excess
equiv.	equivalents
ESI	electrospray ionisation
Et	ethyl
et al.	et alii (and others)
EWG	electron-withdrawing group
g	gram(s)
h	hour(s)
HETCOR	heteronuclear correlation
HMBC	heteronuclear multiple-bond coherence
HMQC	heteronuclear multiple-quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IBX	iodoxybenzoic acid
i.e.	that is (to say)
IR	infrared
J	*J* value
L	litre(s)
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
L_n	ligands
M	moles litre^{-1}
m	multiplet
Mand	mandelate
MBrPA	(1*R*,2*S*,5*R*)-menthyloxy-4-bromo-phenylacetic acid
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl (1,3,5-trimethylbenzyl)
mg	milligram(s)
MHz	megaHertz
min	minutes
mL	millilitre
mmol	millimole
MNA	(1*R*,2*S*,5*R*)-menthyloxy-naphthylacetic acid
mol	moles
MOM	methoxymethyl
m.p.	melting point
MPA	(1*R*,2*S*,5*R*)-menthyloxyphenylacetic acid
Ms	mesyl
MW	microwave

NaBARF	sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NBS	*N*-bromosuccinimde
NFP	*N*-formyl piperidine
NMM	*N*-methyl morpholine
NMR	Nuclear Magnetic Resonance
NPM	*N*-phenylmaleimide
p-ABSA	*para*-acetamidobenzenesulfonyl azide
PCC	pyridinium chlorochromate
pfp	pentafluorophenyl
Ph	phenyl
PMA	phosphomolybdic acid
PMP	*para*-methoxyphenyl
p-NBSA	*para*-nitrobenzenesulfonyl azide
$P(o\text{-tol})_3$	triorthotolyl phosphine
psi	pounds per square inch
P.T.	proton transfer
pybox	pyridine bis(oxazoline)
q	quartet
RCM	ring-closing metathesis
RNA	ribonucleic acid
rt	room temperature
s	singlet
t	triplet
t	tert
TBDMS	tert-butyldimethylsilyl
TBME	*tert*-butyldimethyl ether
td	triplet of doublets
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
$TMSCHN_2$	trimethylsilyl diazomethane
Ts	*p*-toluenesulfonyl (tosyl)
UV	ultraviolet
vs.	versus
W	Watt(s)
WC	Wilkinson's catalyst
D	heat
Å	angstroms
°	degrees

Appendix II Catalyst abbreviations used in Chapter 3

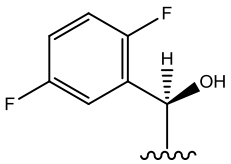


49 Rh_2(*S*-Mand)$_4$
Mand = mandelate

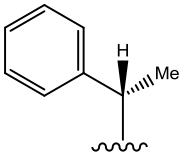


50 X = Cl Rh_2(*R*-*p*-ClMand)$_4$
R-*p*-ClMand = *para*-chloromandelate

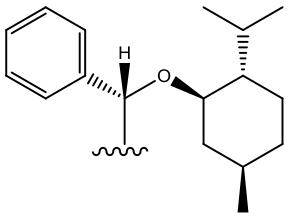
51 X = MeO Rh_2 (*R*-*p*-MeOMand)$_4$
R-*p*-MeOMand = *para*-methoxymandelate



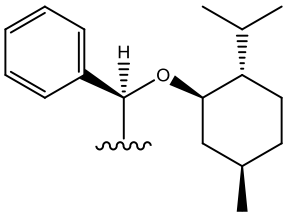
52 Rh_2(*R*-diFMand)$_4$
R-diFMand = 2,5-difluoromandelate



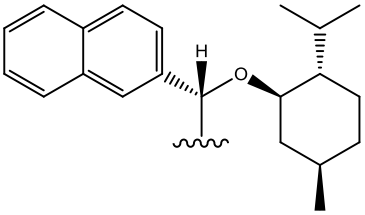
53 Rh_2(*S*-α-Phpa)$_4$
S-α-Phpa = α-phenylpropanoic acid



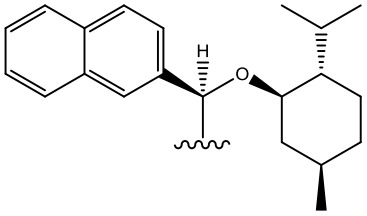
54 Rh_2(*S*-MPA)$_4$
MPA = (1*R*,2*S*,5*R*)-menthyloxyphenylacetic acid



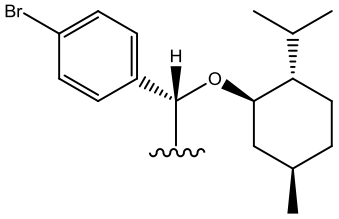
55 Rh_2(*R*-MPA)$_4$
MPA = (1*R*,2*S*,5*R*)-menthyloxyphenylacetic acid



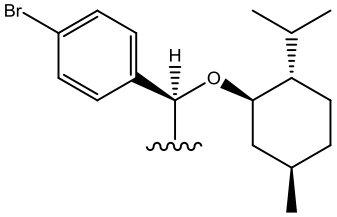
56 Rh_2(*S*-MNA)$_4$
MNA = (1*R*,2*S*,5*R*)-menthyloxynaphthylacetic acid



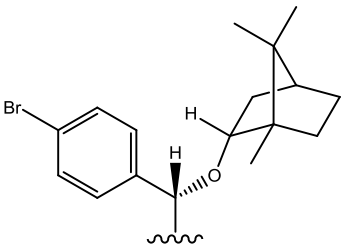
57 Rh_2(*R*-MNA)$_4$
MNA = (1*R*,2*S*,5*R*)-menthyloxynaphthylacetic acid



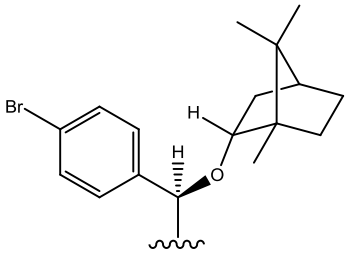
58 Rh_2(*S*-MBrPA)$_4$
MBrPA = (1*R*,2*S*,5*R*)-menthyloxy-4-bromophenylacetic acid



59 Rh_2(*R*-MBrPA)$_4$
MBrPA = (1*R*,2*S*,5*R*)-menthyloxy-4-bromophenylacetic acid

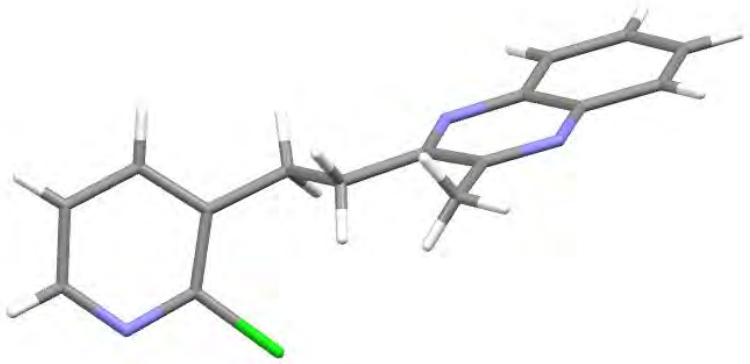


60 Rh_2(*S*-BBrPA)$_4$
BBrPA = borneoloxybrominephenylacetic acid

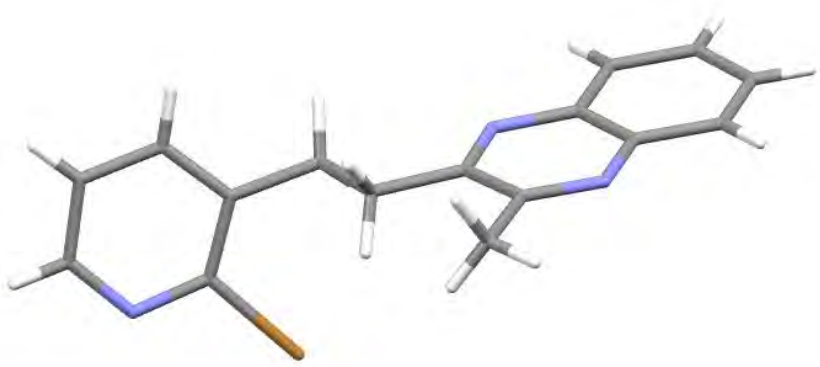


61 Rh_2(*R*-BBrPA)$_4$
BBrPA = borneoloxybrominephenylacetic acid

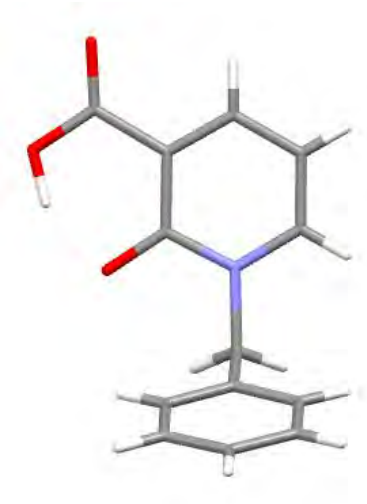
Appendix III X-ray crystal analysis (all compound numbers refer to Chapter 2)



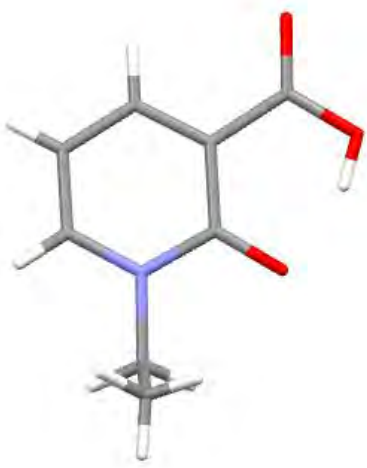
Single crystals of 2-[2-(2-chloropyridin-3-yl)ethyl]-3-methylquinoxaline **227** were grown from deuterated chloroform. Crystal data: $C_{16}H_{14}ClN_3$, M = 283.75, monoclinic, $P2_1/c$, a = 8.3417(3) Å, b = 22.9470(10) Å, c = 7.2431(3) Å, β = 95.2440(10)°, V = 1380.65(10) Å^3, Z = 4, D_c = 1.365 g cm^{-3}, F_{000} = 592, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.98°, μ = 0.269 mm^{-1}, 15959 reflections collected, 2679 unique (R_{int} = 0.0307), final GooF = 2.002, R_1 = 0.0365, wR_2 = 0.0947 (2242 obs. data: $I > 2\sigma(I)$); R_1 = 0.0462 wR_2 = 0.0973 (all data).



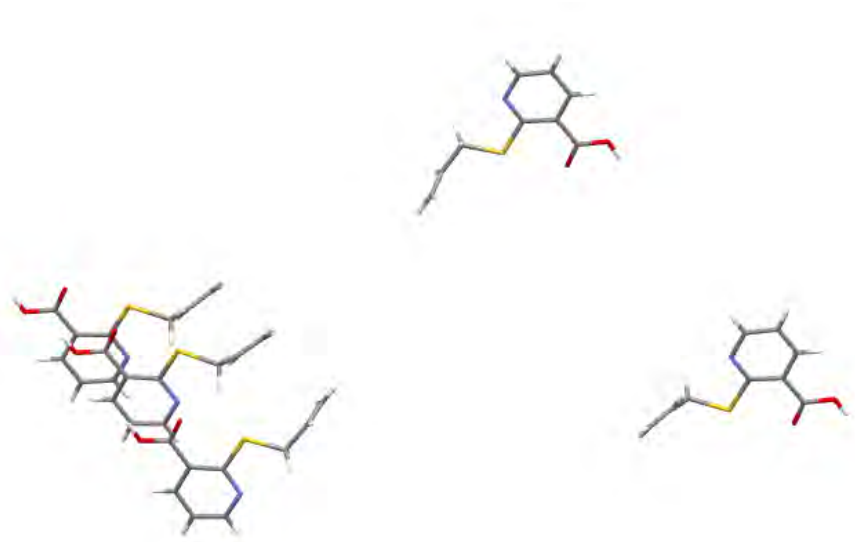
Single crystals of 2-[2-(2-bromopyridin-3-yl)ethyl]-3-methylquinoxaline **232** were grown from deuterated chloroform. Crystal data: $C_{16}H_{14}BrN$, M = 328.21, monoclinic, $P2_1/c$, a = 8.4247(8) Å, b = 23.280(3) Å, c = 7.3012(8) Å, β = 95.430(4)°, V = 1425.5(3) Å^3, Z = 4, D_c = 1.529 g cm^{-3}, F_{000} = 664, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 27.17°, μ = 2.877 mm^{-1}, 16060 reflections collected, 3133 unique (R_{int} = 0.0307), final GooF = 1.028, R_1 = 0.0356, wR_2 = 0.0708 (2369 obs. data: $I > 2\sigma(I)$); R_1 = 0.0555, wR_2 = 0.0769 (all data).



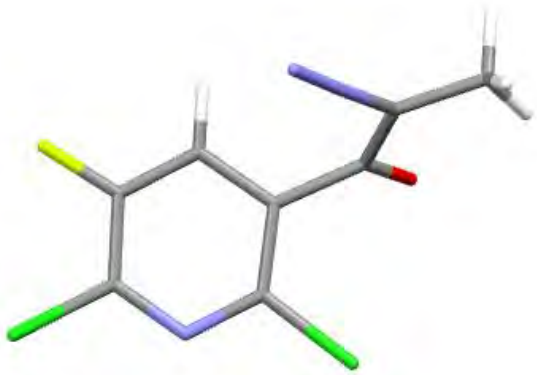
Single crystals of 1-benzyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **122** were grown from deuterated chloroform. Crystal data: $C_{13}H_{11}NO_3$, M = 229.23, monoclinic, $P2_1/n$, a = 4.2977(6) Å, b = 35.811(5) Å, c = 7.4865(11) Å, β = 97.073(4)°, V = 1143.4(3) Å^3, Z = 4, D_c = 1.332 g cm^{-3}, F_{000} = 480, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.04°, μ = 0.096 mm^{-1}, 7133 reflections collected, 2002 unique (R_{int} = 0.0303), final GooF = 1.759, R_1 = 0.0579, wR_2 = 0.1325 (1558 obs. data: $I > 2\sigma(I)$); R_1 = 0.0734, wR_2 = 0.1361 (all data).



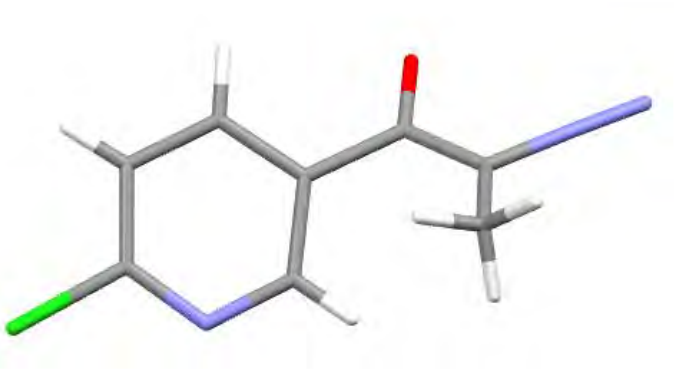
Single crystals of 1-ethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid **124** were grown from deuterated chloroform. Crystal data: $C_8H_9NO_3$, M = 167.16, orthorhombic, $P2_12_12_1$, a = 6.9744(15) Å, b = 10.102(2) Å, c = 11.194(2) ÅV = 788.7(3) Å^3, Z = 4, D_c = 1.408g cm^{-3}, F_{000} = 352, Mo Kα radiation, λ = 0.7107 Å, T = 296(2) K, $2\theta_{max}$ = 26.52°, μ = 0.109 mm^{-1}, 8921 reflections collected, 1642 unique (R_{int} = 0.0440), final GooF = 1.030, R_1 = 0.0424, wR_2 = 0.0962 (1239 obs. data: $I > 2\sigma(I)$); R_1 = 0.0632, wR_2 = 0.1052 (all data).



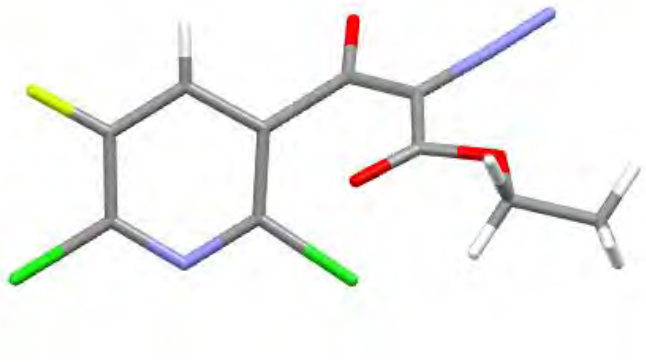
Single crystals of 2-(allylthio)nicotinic acid **125** were grown from deuterated chloroform. Crystal data: $C_9H_9NO_2S$, M = 195.24, monoclinic, $P2_1/n$, a = 7.7731(16) Å, b = 21.637(6) Å, c = 26.663(8) Å, β = 91.004(7)°, V = 4484.(2) Å^3, Z = 20, D_c = 1.446g cm^{-3}, F_{000} = 2040, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.33°, μ = 0.324 mm^{-1}, 49326 reflections collected, 8967 unique (R_{int} = 0.0595), final GooF = 0.940, R_1 = 0.0364, wR_2 = 0.0842 (6525 obs. data: $I > 2\sigma(I)$); R_1 = 0.0642, wR_2 = 0.0999 (all data).



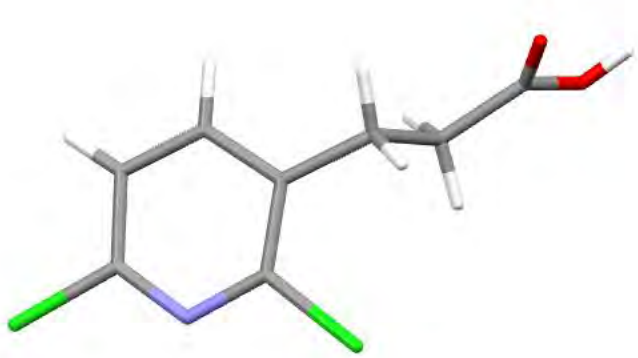
Single crystals of 2-diazo-1-(2,6-dichloro-5-fluoropyridin-3-yl)propan-1-one **65** were grown from deuterated chloroform. Crystal data: $C_8H_4Cl_2FN_3O$, M = 248.04, monoclinic, $P2_1/n$, a = 8.529(5) Å, b = 6.704(3) Å, c = 16.826(10) Å, β = 90.766(16)°, V = 962.0(9) Å^3, Z = 4, D_c = 1.713 g cm^{-3}, F_{000} = 496, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 28.43°, μ = 0.663 mm^{-1}, 13029 reflections collected, 2405 unique (R_{int} = 0.0656), final GooF = 1.057, R_1 = 0.0383, wR_2 = 0.0847 (1873 obs. data: $I > 2\sigma(I)$); R_1 = 0.0582, wR_2 = 0.0934 (all data).



Single crystals of 1-(6-chloropyridin-3-yl)-2-diazopropan-1-one **63** were grown from deuterated chloroform. Crystal data: $C_8H_6ClN_3O$, M = 195.61, monoclinic, $P2_1$, a = 6.8928(8) Å, b = 9.9003(12) Å, c = 6.9862(8) Å, β = 118.607(2), V = 418.55(9) Å^3, Z = 2, D_c = 1.552 g cm^{-3}, F_{000} = 200, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 25.07°, μ = 0.413 mm^{-1}, 8697 reflections collected, 1497 unique (R_{int} = 0.0385), final GooF = 1.060, R_1 = 0.0339, wR_2 = 0.0903 (1453 obs. data: $I > 2\sigma(I)$); R_1 = 0.0347, wR_2 = 0.0909 (all data).



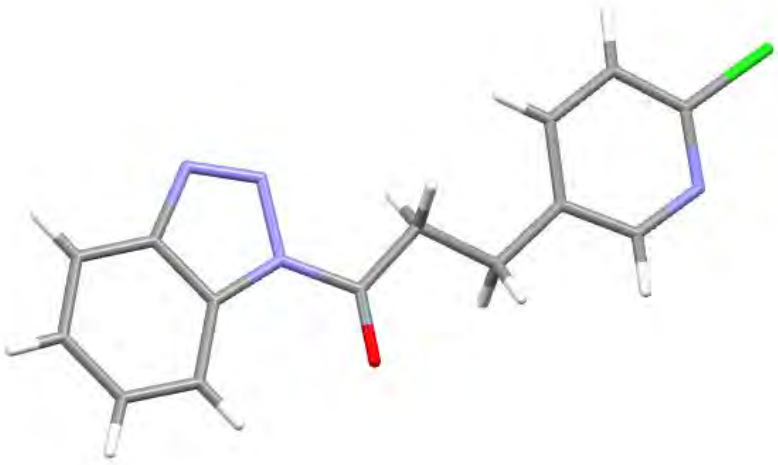
Single crystals of ethyl 2-diazo-3-(2,6-dichloro-5-fluoropyridin-3-yl)-3-oxopropanoate **159** were grown from deuterated chloroform. Crystal data: $C_{10}H_6Cl_2FN_3O_3$, M = 306.08, monoclinic, $P2_1/c$, a = 7.627(6) Å, b = 20.599(18) Å, c = 8.161(7) Å, β = 93.33(3)°, V = 1280.0(18) Å^3, Z = 4, D_c = 1.588 g cm^{-3}, F_{000} = 616, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.11°, μ = 0.526 mm^{-1}, 8908 reflections collected, 2250 unique (R_{int} = 0.1113), final GooF = 0.885, R_1 = 0.0631, wR_2 = 0.1683 (1079 obs. data: $I > 2\sigma(I)$); R_1 = 0.1492, wR_2 = 0.2507 (all data).



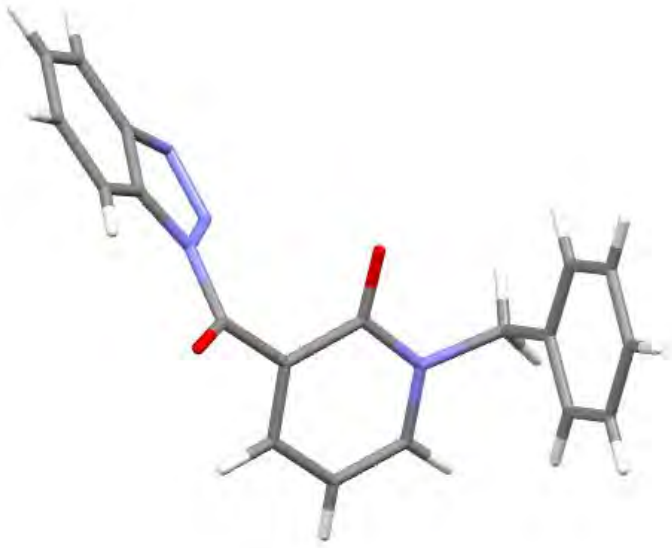
Single crystals of 3-(2,6-dichloropyridin-3-yl)propanoic acid **103** were grown from deuterated chloroform. Crystal data: $C_8H_7Cl_2NO_2$, M = 220.05, monoclinic, $P2_1/c$, a = 17.022(3) Å, b = 4.6952(8) Å, c = 12.127(2) Å, β = 101.411(6)°, V = 950.1(3) Å^3, Z = 4, D_c = 1.538 g cm^{-3}, F_{000} = 448, Mo Kα radiation, λ = 0.7107 Å, T = 300(2) K, $2\theta_{max}$ = 25.03°, μ = 0.647 mm^{-1}, 8470 reflections collected, 1682 unique (R_{int} = 0.1113), final GooF = 0.915, R_1 = 0.0376, wR_2 = 0.0878 (1154obs. data: $I > 2\sigma(I)$); R_1 = 0.0586, wR_2 = 0.0952 (all data).

Single crystals of 3-methyl-2-phenyl-4*H*-pyrano[2,3-b]pyridin-4-one **201*** were grown from deuterated chloroform. Crystal data: $C_{15}H_{11}NO_2$, M = 237.25, monoclinic, $P2_1/n$, a = 3.822(2) Å, b = 20.502(13) Å, c = 13.574(9) Å, β = 95.084(13)°, V = 1059.5(12) Å^3, Z = 4, D_c = 1.487g cm^{-3}, F_{000} = 496, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 25.07°, μ = 0.100 mm^{-1}, 4719 reflections collected, 1729 unique (R_{int} = 0.1453), final GooF = 0.954, R_1 = 0.0817, wR_2 = 0.1926 (885 obs. data: $I > 2\sigma(I)$); R_1 = 0.1598, wR_2 = 0.2400 (all data).

* X-ray crystal structure of **201** is not deemed suitable for publication.



Single crystals of 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-(6-chloropyridin-3-yl)propan-1-one **184** were grown from deuterated chloroform. Crystal data: $C_{14}H_{11}ClN_4O$, M = 286.72, monoclinic, $P2_1/c$, a = 7.445(6) Å, b = 13.049(10) Å, c = 13.882(11) Å, β = 104.051(18), V = 1308.3(18) Å^3, Z = 4, D_c = 1.456 g cm^{-3}, F_{000} = 592, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.67°, μ = 0.293 mm^{-1}, 12116 reflections collected, 2690 unique (R_{int} = 0.0546), final GooF = 1.077, R_1 = 0.0456, wR_2 = 0.1191 (1912 obs. data: $I > 2\sigma(I)$); R_1 = 0.0708, wR_2 = 0.1382 (all data).



Single crystals of 3-(1*H*-benzo[d][1,2,3]triazole-1-carbonyl)-1-benzylpyridin-2(1*H*)-one **189** were grown from deuterated chloroform. Crystal data: $C_{19}H_{14}N_4O_2$, M = 330.34, monoclinic, $P2_1/c$, a = 5.7573(7) Å, b = 10.3774(12) Å, c = 25.578(3) Å, β = 93.948(5), V = 1524.6(3) Å^3, Z = 4, D_c = 1.439 g cm^{-3}, F_{000} = 688, Mo Kα radiation, λ = 0.7107 Å, T = 100(2) K, $2\theta_{max}$ = 26.48°, μ = 0.097 mm^{-1}, 17008 reflections collected, 3128 unique (R_{int} = 0.0479), final GooF = 1.266, R_1 = 0.0372, wR_2 = 0.0838 (2433 obs. data: $I > 2\sigma(I)$); R_1 = 0.0547, wR_2 = 0.0905 (all data).

Appendix IV Chiral stationary phase HPLC data (all compound numbers refer to Chapter 3)

- Chiral HPLC conditions for the *trans* cyclopropane **78** (*E*), as well as *trans* and *cis* dihydrobenzofurans **117** and **118** from reactions in the presence of a range of rhodium(II) catalysts were investigated The corresponding previously reported chiral stationary phase HPLC data, as well as conditions previously employed in the literature are summarised below (**Table 1**), for comparative purposes.

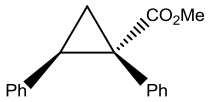
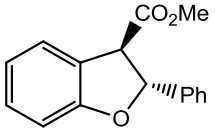
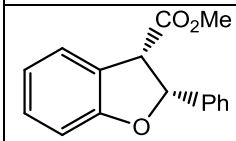
- Samples for chiral stationary phase HPLC analysis were prepared at a concentration of ~1.0 mg/mL.

- Stereochemical assignments of known cyclopropane **78** (*E*) and dihydrobenzofurans **117** and **118** were made by comparison to previously reported chiral stationary phase HPLC data[1-3] and polarimetry data for the purified dihydrobenzofurans **117** and **118** in **Section 3.5** (**Table 3.18**, entry 14).[3]

- All chiral stationary phase HPLC analysis was conducted at room temperature unless otherwise stated.

- Notably, the retention times can change per injection (particularly for long run times) and the retention times differ slightly with respect to reported data.[3] However, the enantiomeric sequence remains consistent.

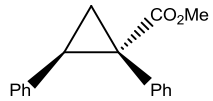
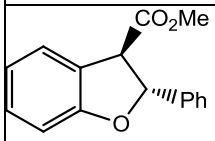
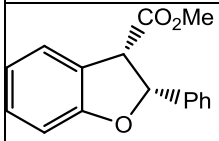
Table 1: HPLC conditions for intermolecular cyclopropanation product 78 (*E*) **and intramolecular C–H insertion products 117 and 118 previously reported in the literature.**

Compound	Column[a]	λ (nm)	Flow Rate (mL/min)	Injection Volume (μL)	Mobile Phase IPA : Hexane	Retention Time (min)
 **78** (*E*)	Chiralpak OJ-H	210 nm	1.0 mL/min	10.0	1 : 99	–[4,b]
 **117**	Chiralpak OJ-H	254 nm	1.0 mL/min	10.0	10 : 90	**10.3 (major, 2*R*,3*R*)-(–)**[3] **15.0 (minor, 2*S*,3*S*)**[3]
 **118**	Chiralcel OD-H	254 nm	1.0 mL/min	10.0	10 : 90	**9.8 (major, 2*R*,3*S*)-(+)**[3] **17.8 (minor, 2*S*,3*R*)**[3]

[a] Resolution of compounds was achieved using a Chiralpak OJ-H or a Chiralcel OD-H column.

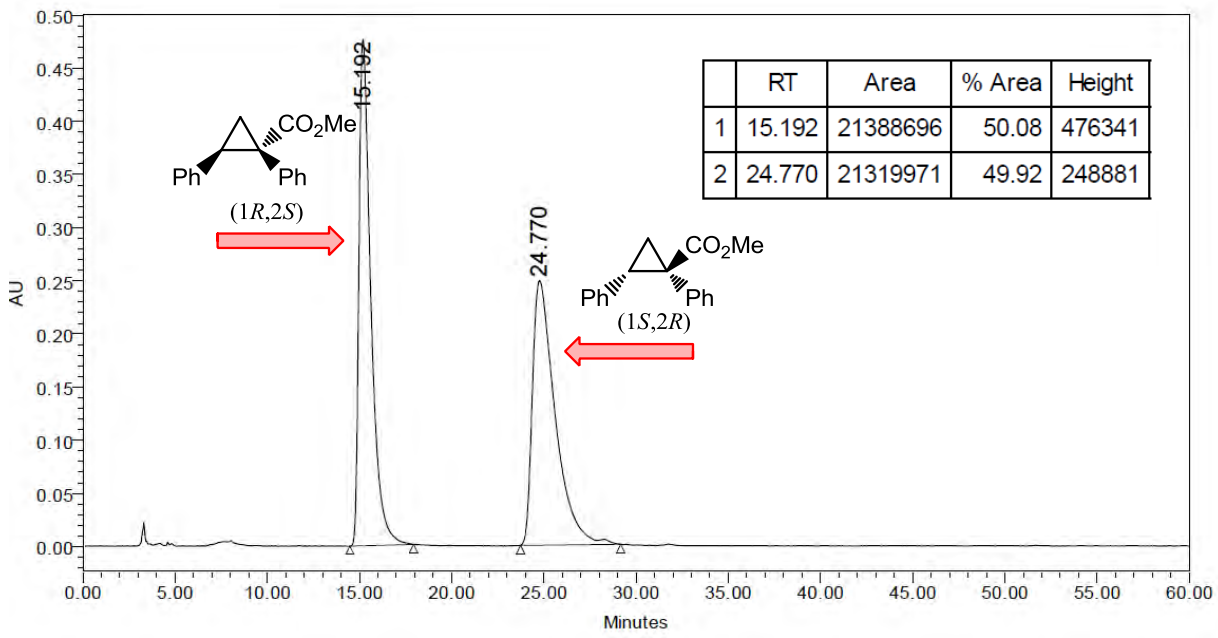
[b] Retention times not provided by Bayordan using these conditions but claim that confirmation of enantiomers was determined by comparison of retention times with those of authentic samples.[4] Davies has reported retention times for **78** (*E*) using chiral stationary phase HPLC, though these were carried out on (*R*,*R*)-Whelk and (*S*,*S*)-Whelk columns in comparison to Chiralpak OJ-H column used in this work.[5,6]

Table 2: HPLC conditions for intermolecular cyclopropanation product 78 (*E*) and intramolecular C–H insertion products 117 and 118 carried out in this project

Compound	Column[a]	λ (nm)	Flow Rate (mL/min)	Injection Volume (μL)	Mobile Phase IPA : Hexane	Retention Time (min)
 **78** (*E*)	Chiralpak OJ-H	210 nm	1.0 mL/min	10.0	1 : 99	**15.8 (minor, 1*R*,2*S*)** **25.8 (major, 1*S*,2*R*)**
 **117**	Chiralpak OJ-H	254 nm	1.0 mL/min	10.0	10 : 90	**12.8 (major, 2*R*,3*R*)-(–)** **17.2.0 (minor, 2*S*,3*S*)**
	Chiralcel OD-H	254 nm	1.0 mL/min	10.0	10 : 90	**5.4 (minor, 2*R*,3*R*)** **6.5 (major, 2*S*,3*S*)**
 **118**	Chiralcel OD-H	254 nm	1.0 mL/min	10.0	10 : 90	**9.0 (major, 2*R*,3*S*)-(+)** **16.3 (minor, 2*S*,3*R*)**

[a] Resolution of compounds was achieved using a Chiralpak OJ-H or Chiralcel OD-H column

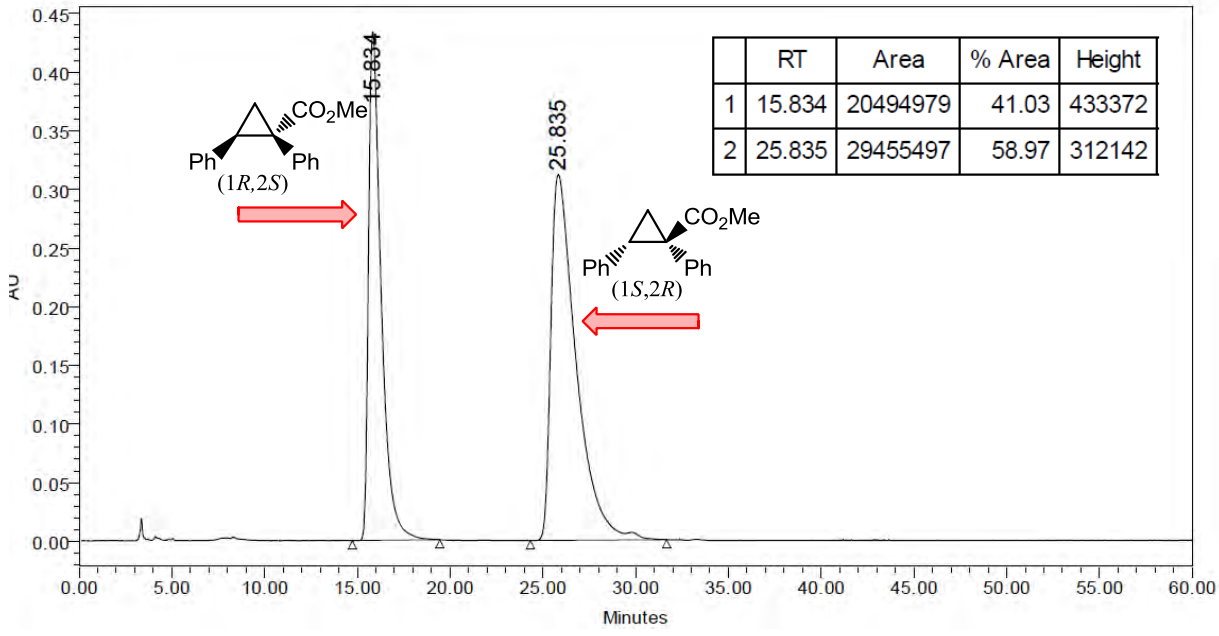
(±)-*trans*-Methyl 1,2-diphenylcyclopropanecarboxylate 78 (*E*)



	RT	Area	% Area	Height
1	15.192	21388696	50.08	476341
2	24.770	21319971	49.92	248881

Figure 1: Isolated from reaction of 76 in the presence of $Rh_2(OAc)_4$ (Table 3.15, entry 2)

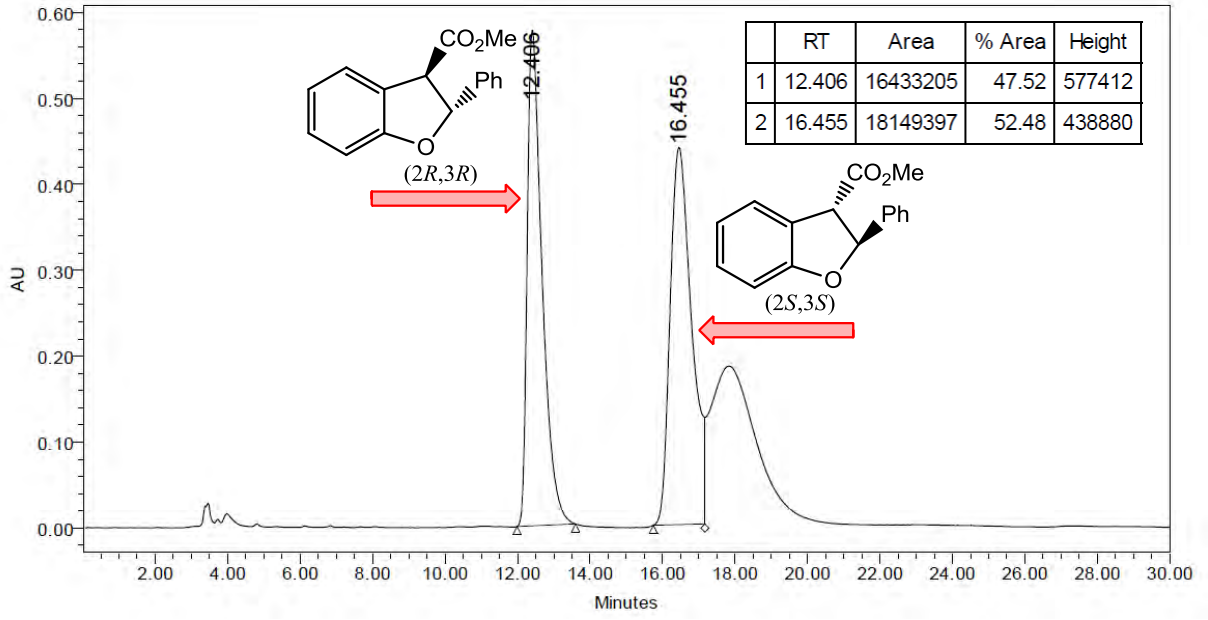
(1*R*,2*S*)-Methyl 1,2-diphenylcyclopropanecarboxylate 78 (*E*)



	RT	Area	% Area	Height
1	15.834	20494979	41.03	433372
2	25.835	29455497	58.97	312142

Figure 2: Isolated from reaction of 76 in the presence of Rh_2('A'-BBrPA)$_4$ (Table 3.15, entry 17) (18% ee)

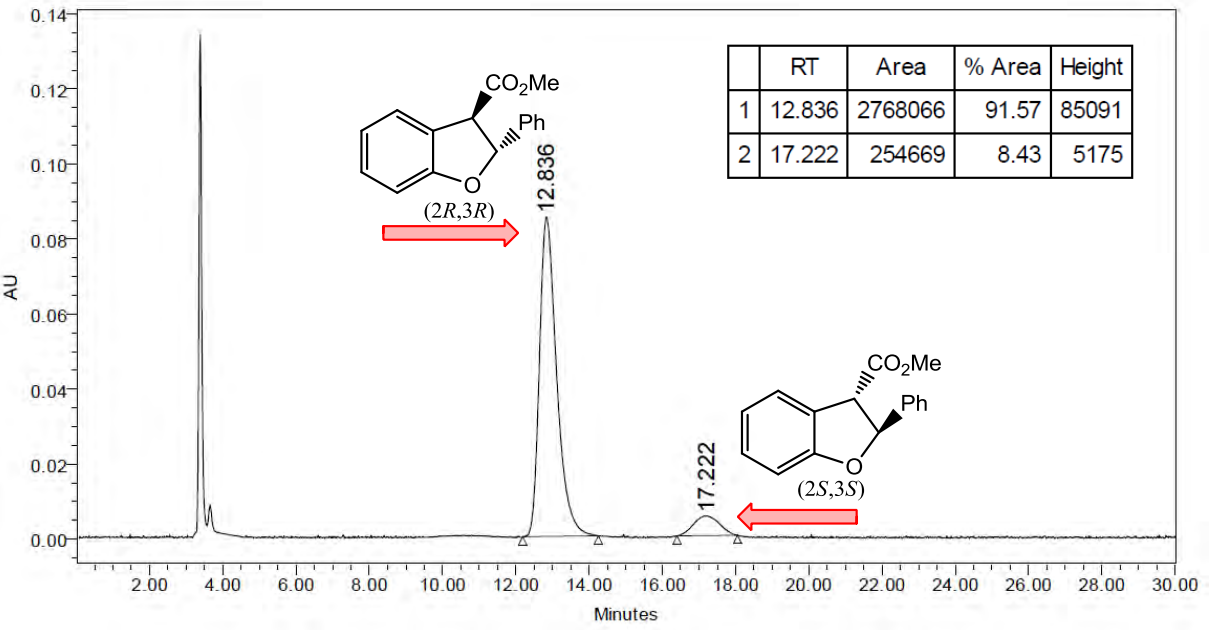
(±)-*trans*-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 117



	RT	Area	% Area	Height
1	12.406	16433205	47.52	577412
2	16.455	18149397	52.48	438880

Figure 3: Isolated from reaction of 111 in the presence of $Rh_2(OAc)_4$ (Table 3.18, entry 1)

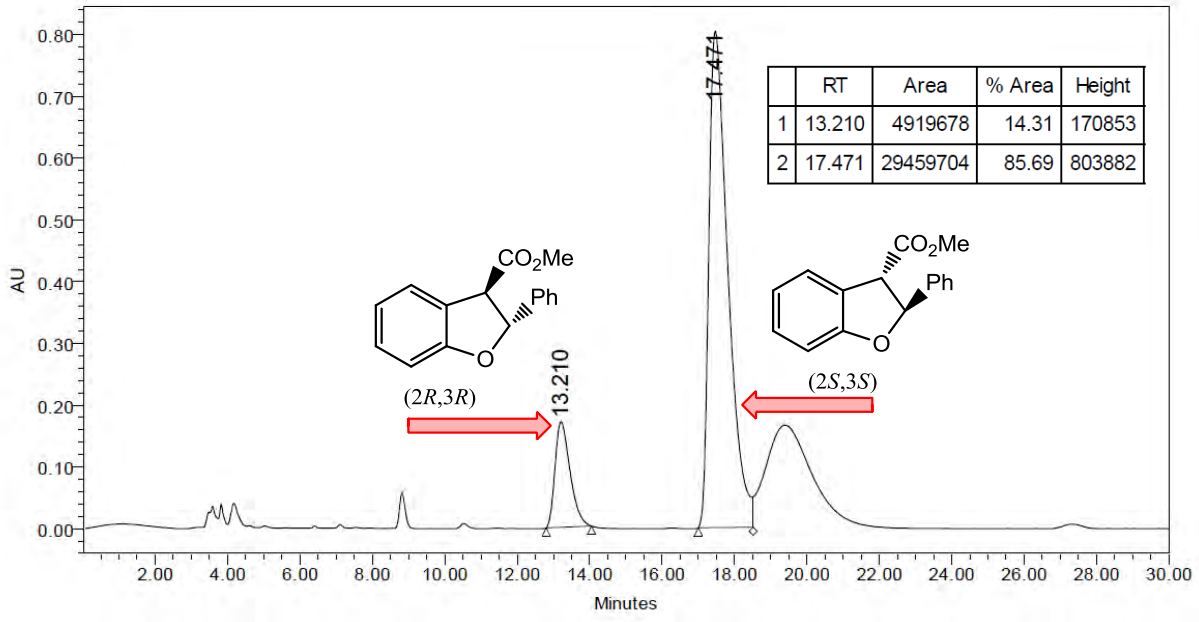
(2*R*,3*R*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 117



	RT	Area	% Area	Height
1	12.836	2768066	91.57	85091
2	17.222	254669	8.43	5175

Figure 4: Isolated from reaction of 116 in the presence of Rh_2('A'-MPA)$_4$ (Table 3.18, entry 12) (83% ee)

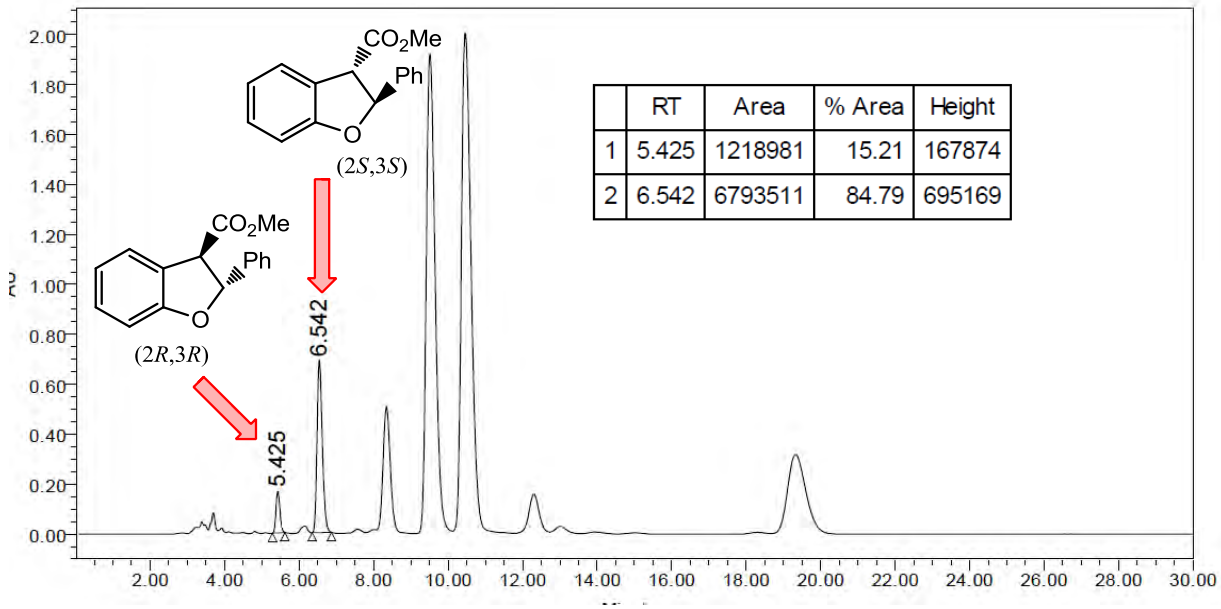
(2*S*,3*S*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 117



	RT	Area	% Area	Height
1	13.210	4919678	14.31	170853
2	17.471	29459704	85.69	803882

Figure 5: Isolated from reaction of 116 in the presence of Rh_2('B'-MBrPA)$_4$ (Table 3.18 entry 22) and run on the Chiralpak OJ-H column

(2*S*,3*S*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 117



	RT	Area	% Area	Height
1	5.425	1218981	15.21	167874
2	6.542	6793511	84.79	695169

Figure 6: Isolated from reaction of 116 in the presence of Rh_2('B'-MPA)$_4$ (Table 3.18, entry 22) (70% ee) and run on the Chiralcel OD-H column

(±)-*cis*-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 118

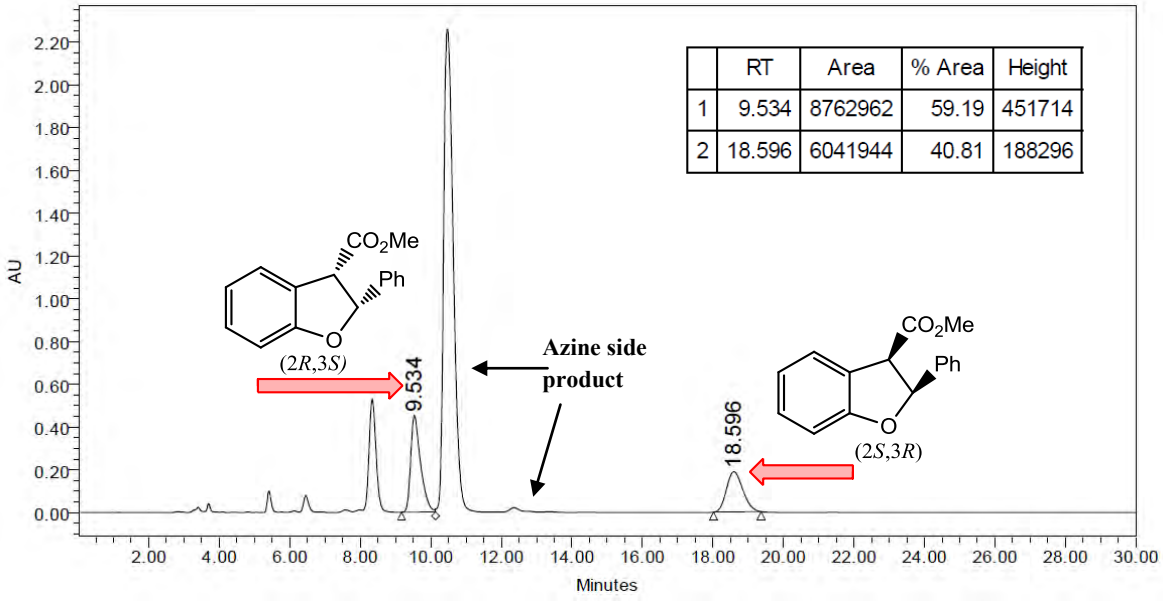


Figure 7: Isolated from reaction of 116 in the presence of $Rh_2(OAc)_4$ (Table 3.18, entry 1)

(2*R*,3*S*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 118

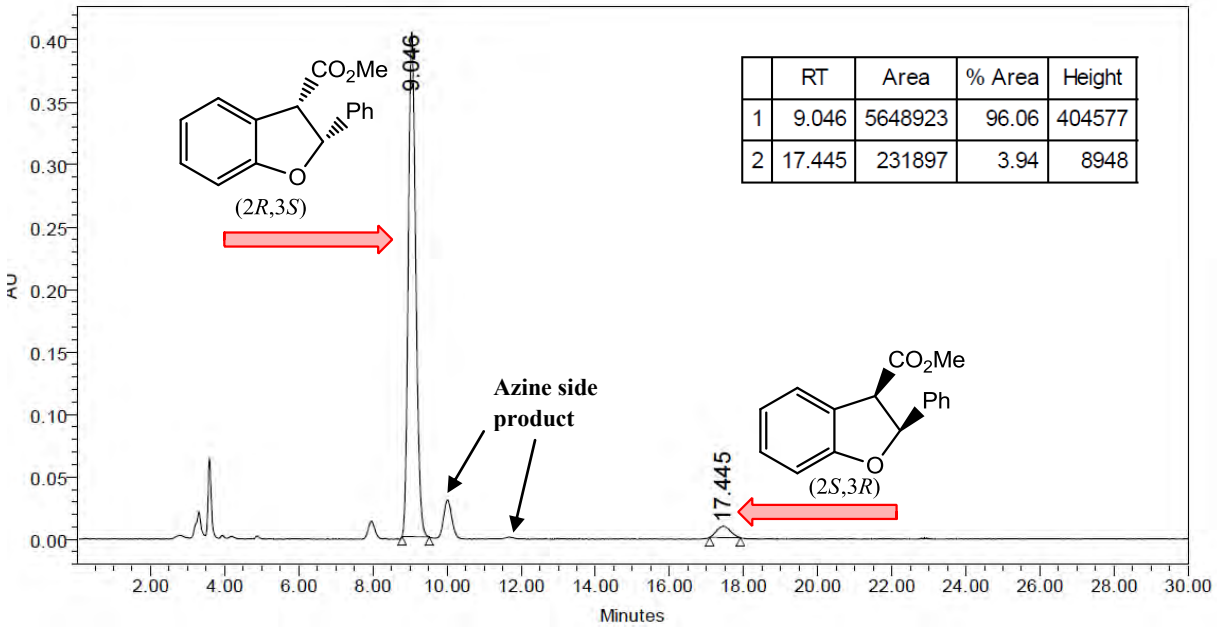


Figure 8: Isolated from reaction of 116 in the presence of Rh_2(*S*-PTTL)$_4$ (Table 3.18, entry 3) (92% ee)

(2*S*,3*R*)-Methyl 2-phenyl-2,3-dihydrobenzofuran-3-carboxylate 118

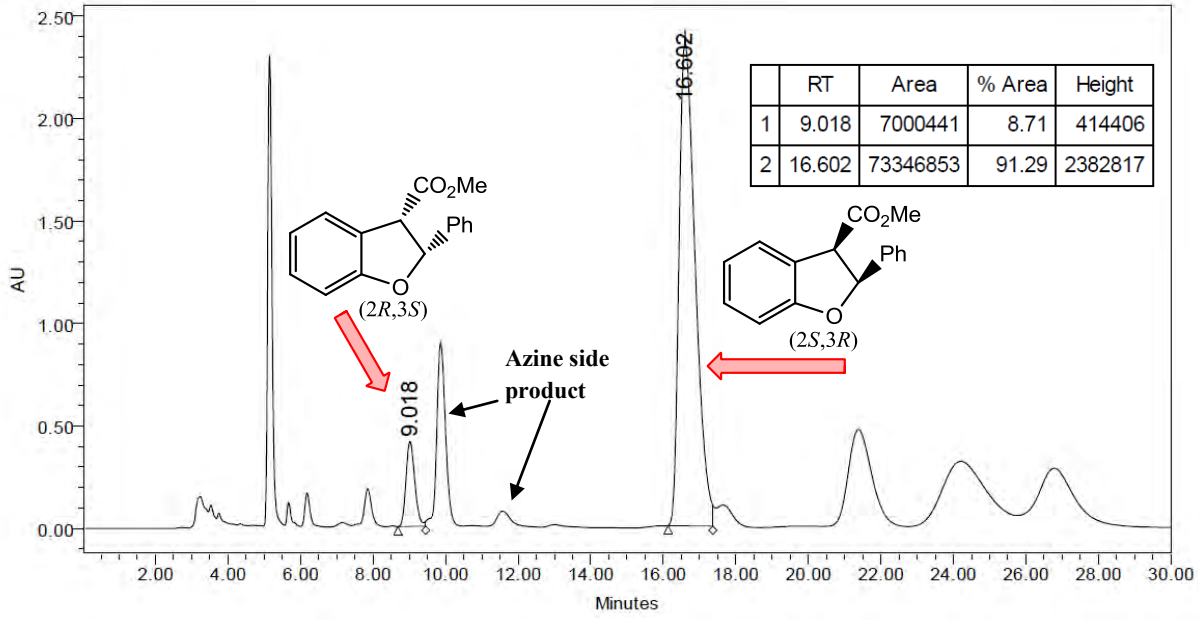


Figure 9: Isolated from reaction of 116 in the presence of Rh_2('A'-MPA)$_4$ (Table 3.18, entry 13) (83% ee)

Appendix V **2D NMR experiments for structural assignment (all compound numbers refer to Chapter 2)**

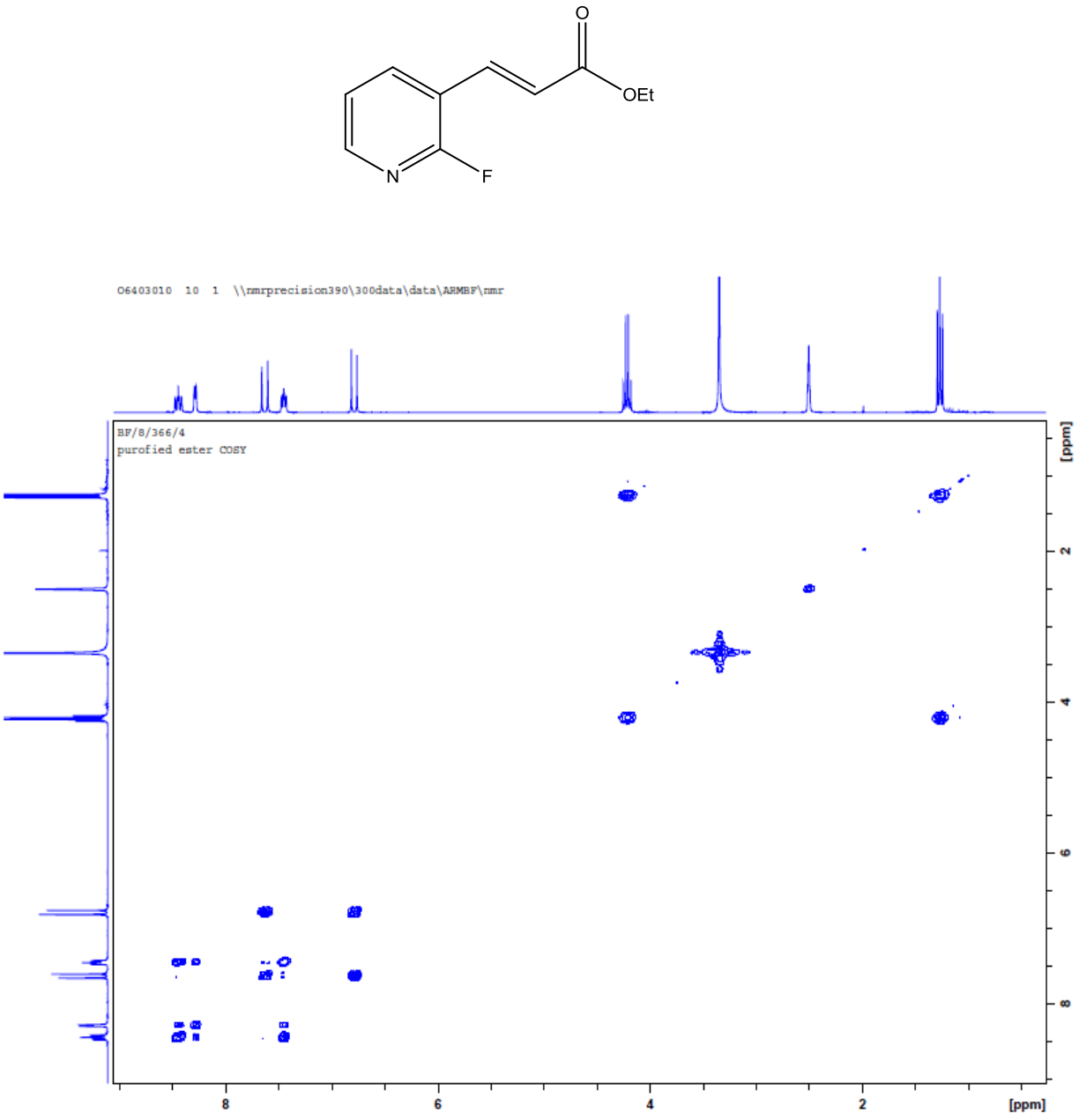


Figure 8 ^{1}H–^{1}H COSY (300 MHz, DMSO-d_6) spectrum of 79

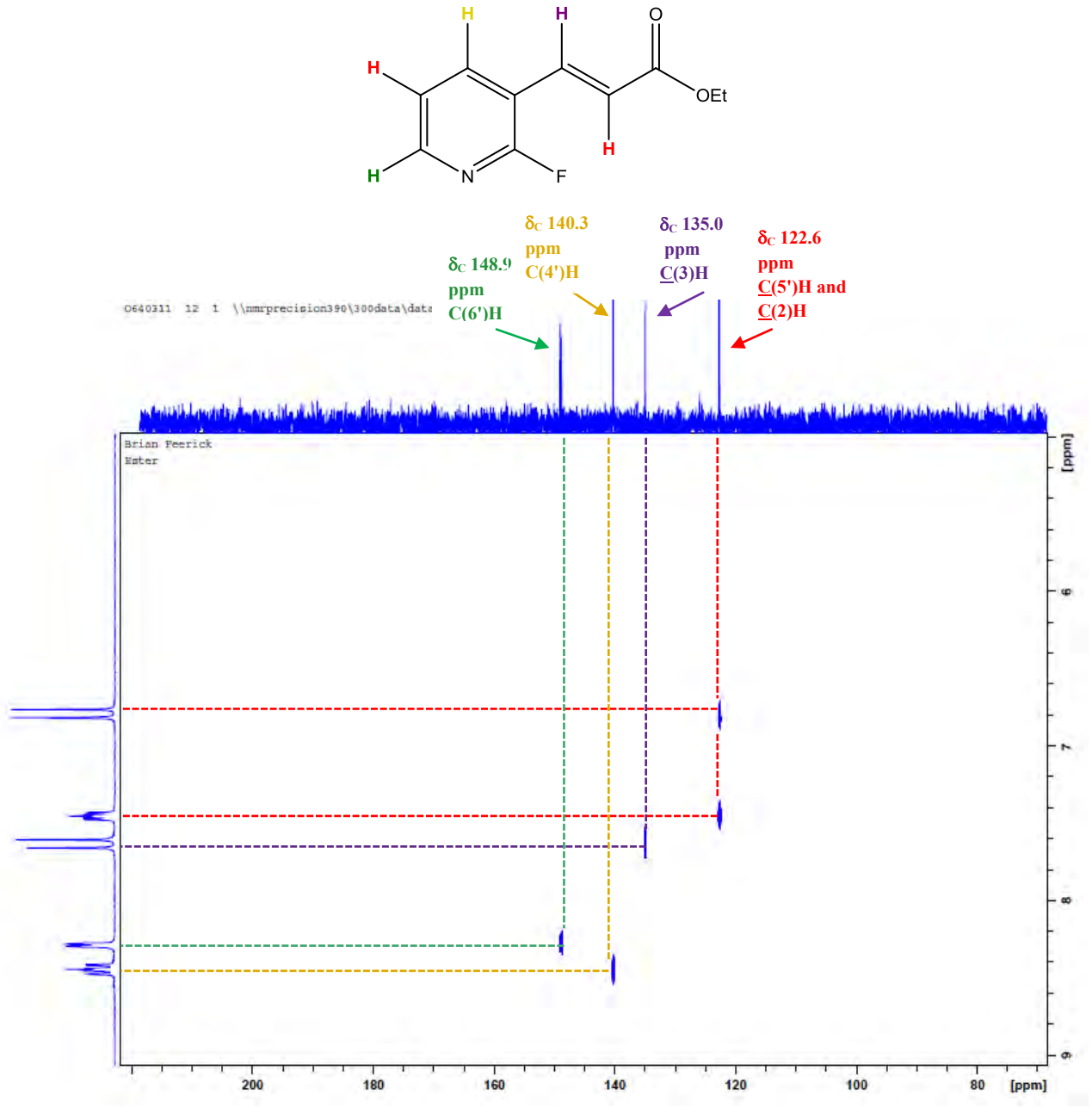
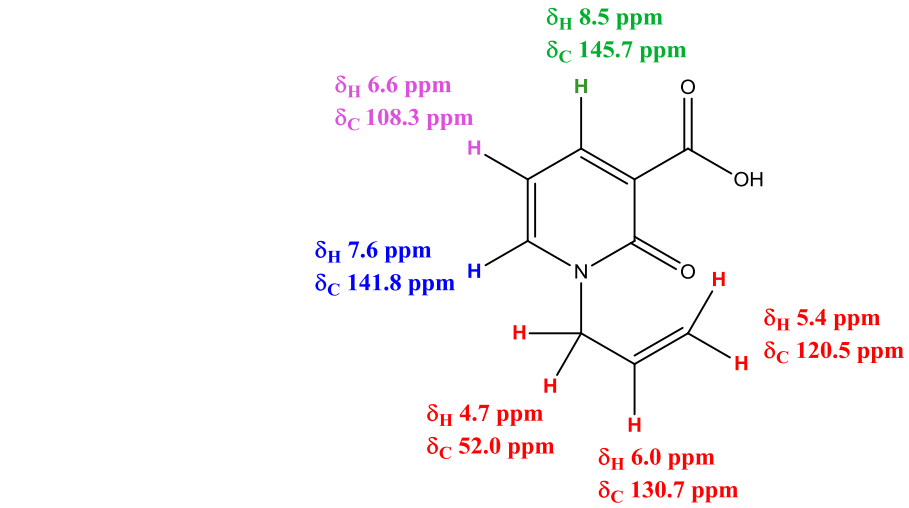


Figure 9: $^{1}H–^{13}C$ HETCOR (300 MHz and 75.5 MHz, DMSO-d_6) spectrum of 79



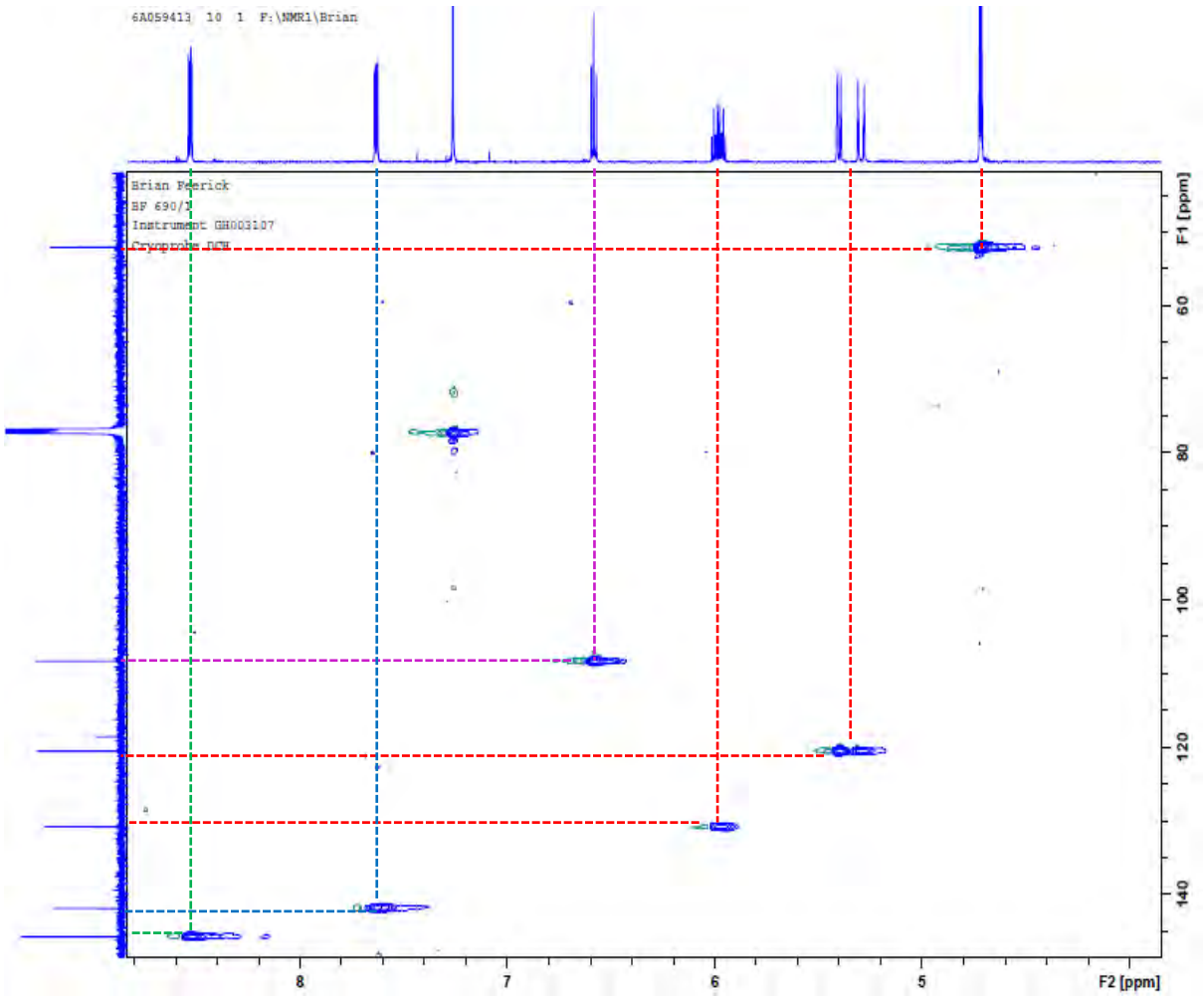


Figure 10: ^{1}H–^{13}C HSQC (600 MHz and 150.9 MHz, $CDCl_3$) spectrum of 119

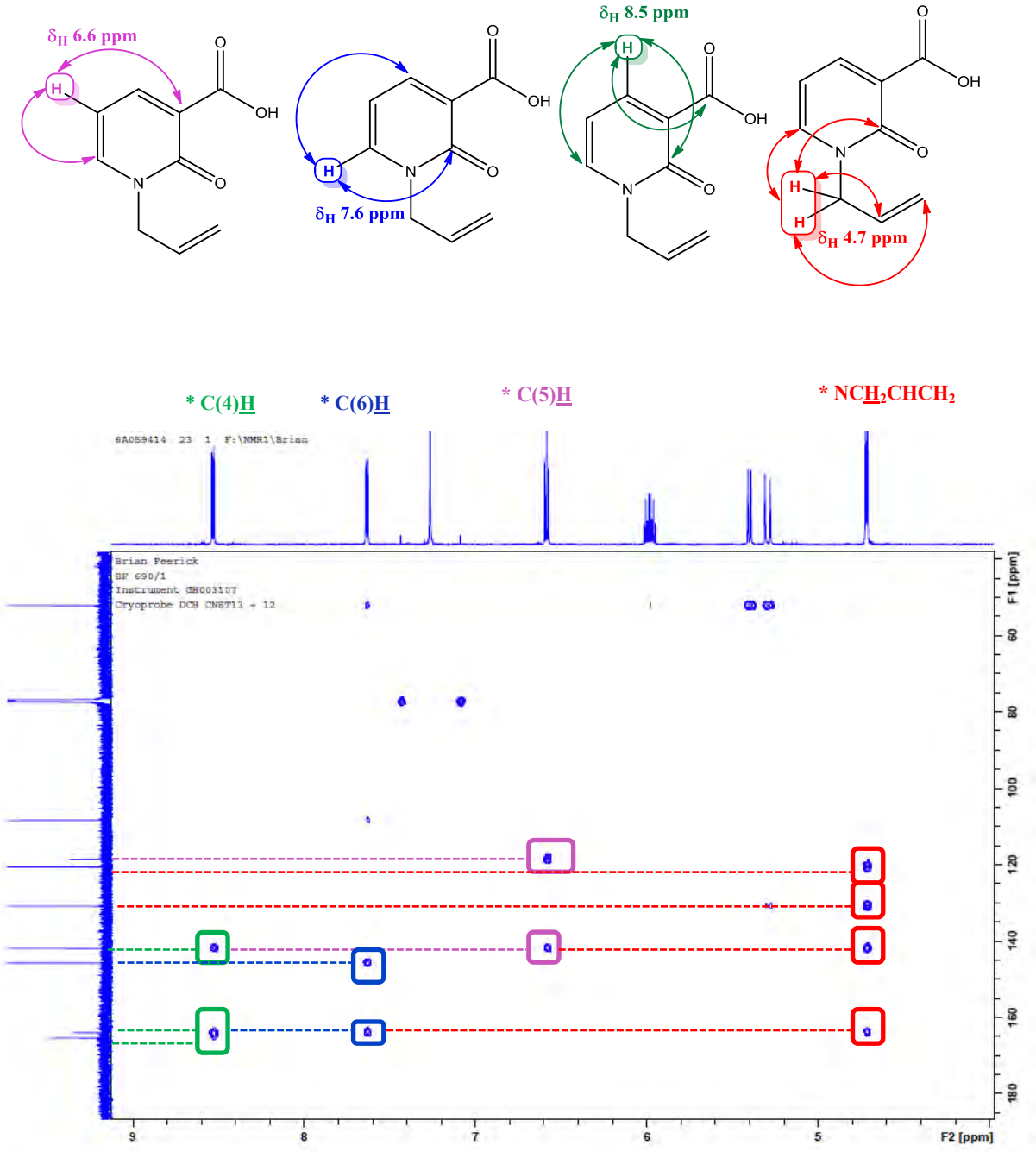


Figure 11: $^{1}H–^{13}C$ HMBC (600 MHz and 150.9 MHz, $CDCl_3$) connectivities of 119

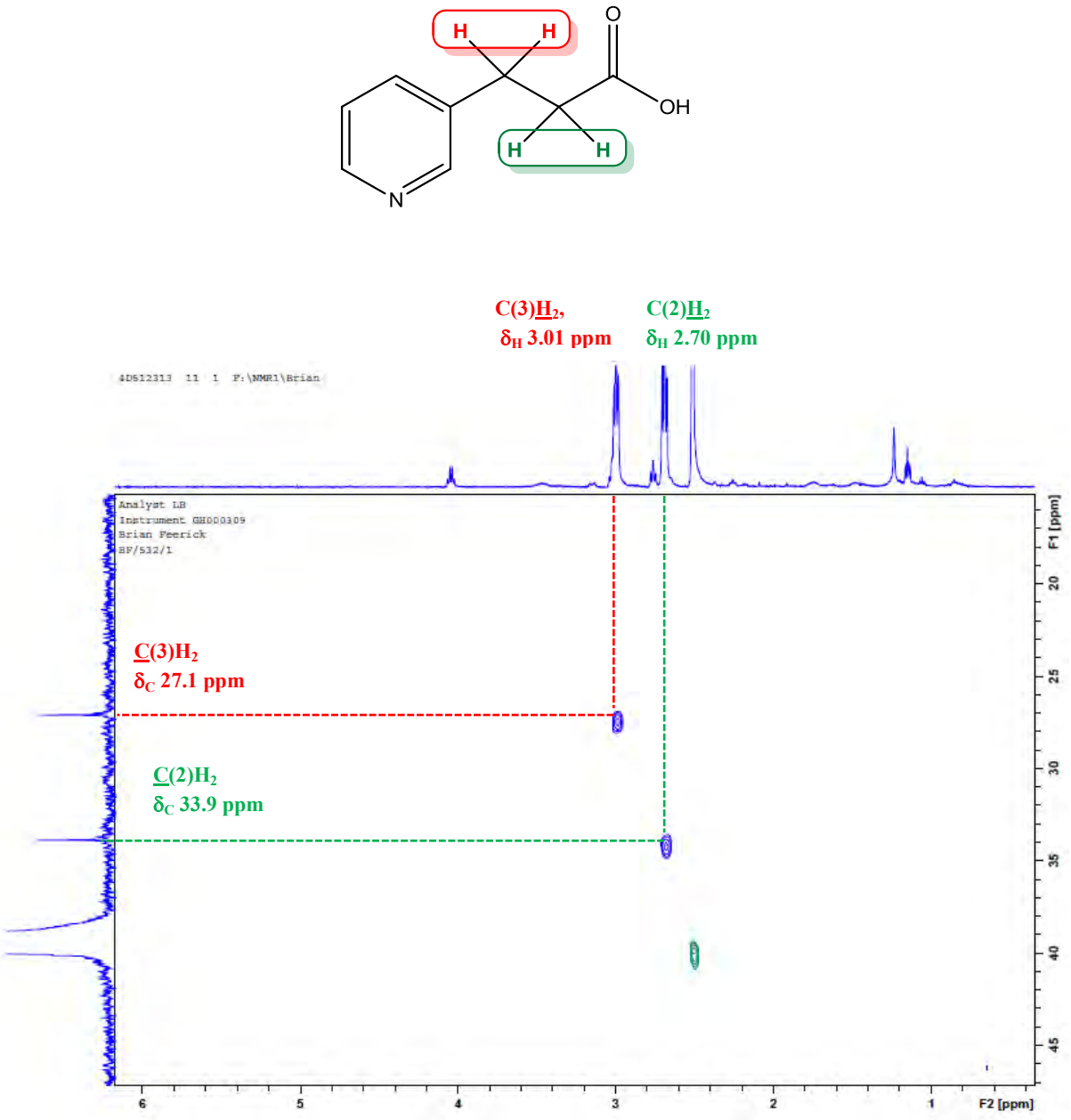


Figure 12: $^{1}H–^{13}C$ HSQC (500 MHz and 125.8 MHz, DMSO-d_6) spectrum of 47

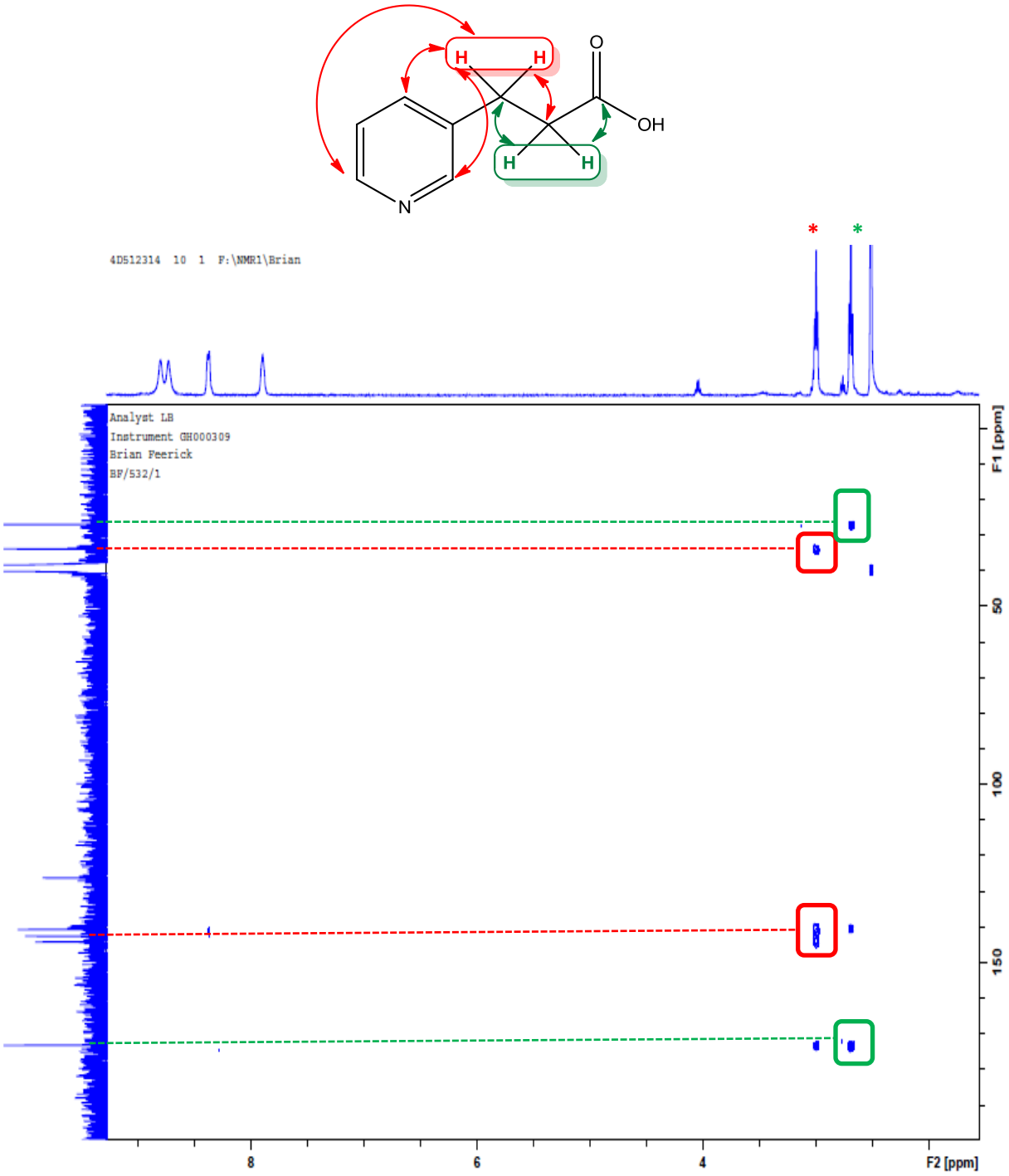


Figure 13: ^{1}H–^{13}C HMBC (500 MHz and 125.8 MHz, DMSO-d_6) connectivities of 47

Reference List

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